A Dissertation on

CLINICOPATHOLOGICAL CORRELATION OF CUTANEOUS VASCULITIDES

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I **Dr. KRISHNA MEERA M.S** solemnly declare that the dissertation entitled **"CLINICOPATHOLOGICAL CORRELATION OF CUTANEOUS VASCULITIDES"** is a bonafide work done by me at Coimbatore Medical College Hospital during the year June 2016 to May 2017 under the guidance & supervision of **Dr.M.Revathy M.D (Derm),** Professor & Head of Department, Department of Dermatology, Coimbatore Medical College & Hospital. The dissertation is submitted to Dr.MGR Medical University towards partial fulfillment of requirement for the award of MD degree branch XII Dermatology, Venereology and Leprology.

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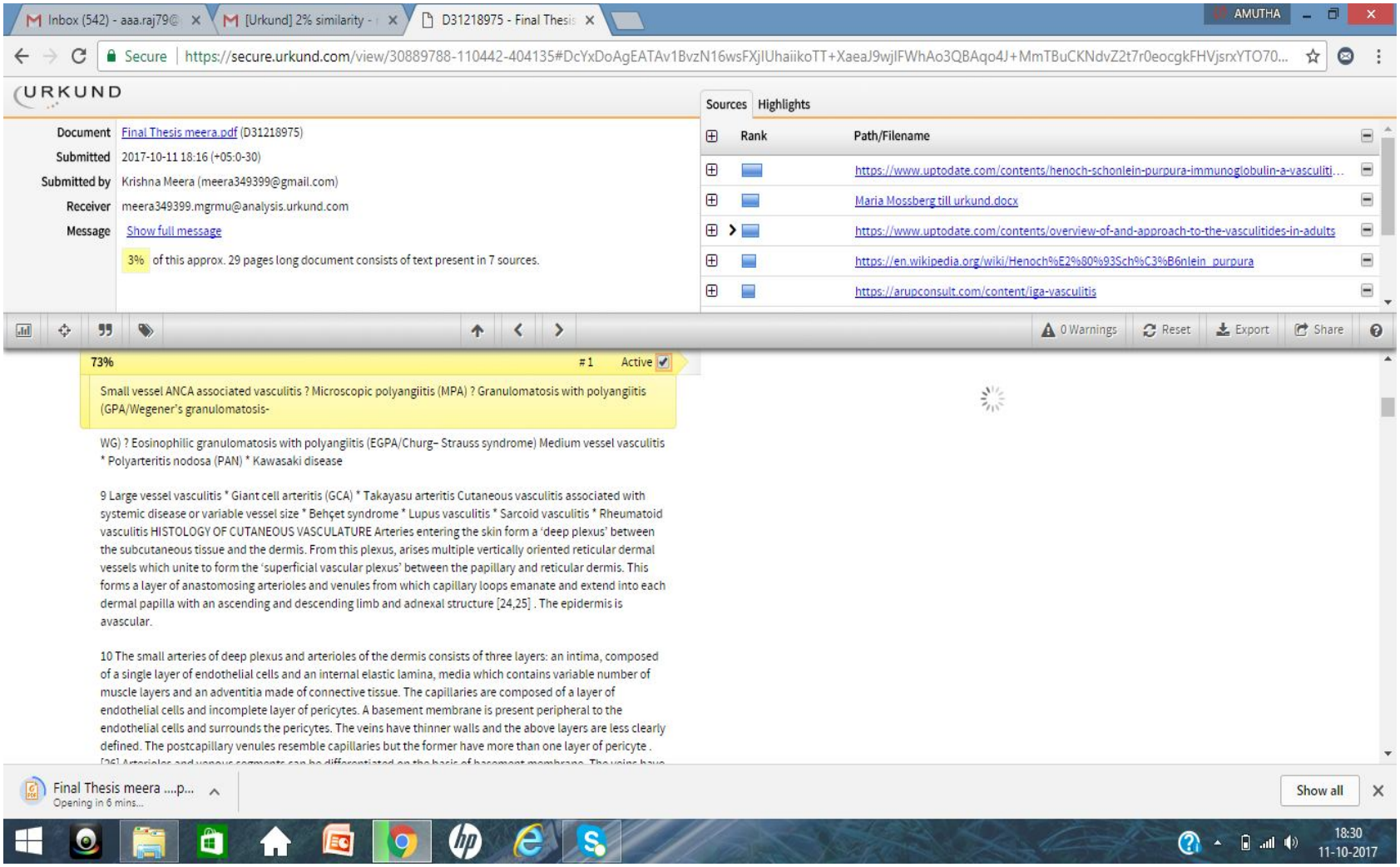
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WG) ? Eosinophilic granulomatosis with polyangiitis (EGPA/Churg– Strauss syndrome) Medium vessel vasculitis * Polyarteritis nodosa (PAN) * Kawasaki disease
9 Large vessel vasculitis * Giant cell arteritis (GCA) * Takayasu arteritis Cutaneous vasculitis associated with systemic disease or variable vessel size * Behçet syndrome * Lupus vasculitis * Sarcoid vasculitis * Rheumatoid vasculitis HISTOLOGY OF CUTANEOUS VASCULATURE Arteries entering the skin form a 'deep plexus' between the subcutaneous tissue and the dermis. From this plexus, arises multiple vertically oriented reticular dermal vessels which unite to form the 'superficial vascular plexus' between the papillary and reticular dermis. This forms a layer of anastomosing arterioles and venules from which capillary loops emanate and extend into each dermal papilla with an ascending and descending limb and adnexal structure [24,25] . The epidermis is avascular.
10 The small arteries of deep plexus and arterioles of the dermis consists of three layers: an intima, composed of a single layer of endothelial cells and an internal elastic lamina, media which contains variable number of muscle layers and an adventitia made of connective tissue. The capillaries are composed of a layer of endothelial cells and incomplete layer of pericytes. A basement membrane is present peripheral to the endothelial cells and surrounds the pericytes. The veins have thinner walls and the above layers are less clearly defined. The postcapillary venules resemble capillaries but the former have more than one layer of pericyte .
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LIST OF ABBREVIATIONS

CHCC	-	Chapel Hill Consensus Conference
ACR	-	American College of Rheumatology
LCV	-	Leukocytoclastic vasculitis
CSVV	-	Cutaneous small vessel vasculitis
HUV	-	Hypocomplementemic urticarial vasculitis
HSO	-	Henoch–Schönlein purpura
Anti-GBM	-	Anti Glomerular basement membrane
ANCA	-	Anti neutrophil cytoplasmic antibodies
MPA	-	Microscopic polyangiitis
GPA	-	Granulomatosis with polyangiitis
WG	-	Wegener's granulomatosis
EGPA	-	Eosinophilic granulomatosis with polyangiitis
PAN	-	Polyarteritis nodosa
GCA	-	Giant cell arteritis
GMP	-	Granule membrane protein
Ig	-	Immunoglobulin
EED	-	Erythema elevatum diutinum
CTD	-	Connective tissue disease.
MPO	-	myeloperoxidase
PR3	-	Proteinase 3

IBD	-	Inflammatory bowel disease
HIV	-	Human immunodeficiency virus
GI	-	Gastrointestinal
SLE	-	Systemic lupus erythematosus
RF	-	Rheumatoid factor
PAS	-	Periodic acid schiff
UV	-	Urticarial vasculitis
HUV	-	Hypocomplementemic urticarial vasculitis
NC1 domain	-	Non collagenous domain
TNF	-	Tumour necrosis factor
ESR	-	Erythrocyte sedimentation rate
ANA	-	Anti nuclear antibody
APLA	-	Antiphospholipid antibody
ASO	-	Antistreptolysin O
CRP	-	C-reactive protein
RBC	-	Red blood cell
EMF	-	Erythema multiforme
ATT	-	Antituberculous therapy
CSOM	-	Chronic suppurative otitis media
CBC	-	Complete blood count
RFT	-	Renal function test
LFT	-	Liver function test

LDH	-	Lactate dehydrogenase
PCOS	-	Polycystic ovarian syndrome
OGD scopy	-	Oesophago-gastro deuodenoscopy
LV	-	Lymphocytic vasculitis
DIF	-	Direct immunofluorescence
CMCH	-	Coimbatore Medical College and Hospital
PS	-	Peripheral smear

INTRODUCTION

The term ‘vasculitis’ refers to segmental inflammation of the wall of a blood vessel or lymph vessel. Skin, being the largest organ in the body, is well supplied by blood vessels. Cutaneous vasculitis refers to the inflammation of these cutaneous blood vessels, resulting in blood flow alterations, ischemia and damage[1]. The disease can involve any type of blood vessel, with the post-capillary venules being the most frequently affected[2]. Often, the disease is part of a generalised disease of the blood vessel wall, and skin manifestation is the initial presentation of the generalised disease process. This makes the role of the dermatologist paramount in the diagnosis and further management of these disorders.

The disease is extensively discussed in dermatology literature, but is often the most poorly understood. Etiopathogenesis of many of the cutaneous vasculitides are not known. Drug intake or infections may act as antigenic triggers in many cases. (The time interval between exposure to a trigger and onset of vasculitis is usually 7-10 days.) Underlying disorders like connective tissue

diseases, inflammatory bowel diseases (IBD) or internal malignancies may be the causative factor in many cases [3].

According to Carlson et al, the incidence of this disease entity ranges from 15.4 to 29.7 cases per million population per year. The disease affects people of all ages - is more common in adults than in children. In children, 90% of cases present with Henoch-Schonlein purpura. In the adult population, the mean age of onset of disease is 47 years. In the pediatric population, the mean age is 7 years. Regarding sex predilection, the disease affects females more commonly by a narrow margin[4] .

There are multiple classification systems described in literature for cutaneous vasculitis. Of these, the Chapel Hill Consensus conference (CHCC) classification and the American College of Rheumatology (ACR) classification are the most widely used. The CHCC classification is based on pathological criteria. The ACR classification is based predominantly on clinical findings [4].

Clinically, vasculitis can present with an array of manifestations which in turn depends upon the size of vessel involved. The most common cutaneous manifestation is palpable purpura. In many instances this remains the only manifestation. Other

cutaneous manifestations include papules, nodules, vesicles, pustules and/or vesiculo-bullous lesions. Lesions may progress to ulcerative necrotic lesions which heal with post-inflammatory pigmentation. Livedo reticularis, a manifestation characterised by net-like pattern of mottled red or blue discoloration, is another presenting feature of vasculitis. This lesion is seen typically in lower legs (in regions prone to stasis). Cutaneous manifestations may be accompanied by systemic symptoms like fever, anorexia, arthralgia and/or myalgia[5]. The clinical features seen in individual vasculitis is discussed in more detail in the subsequent sections.

We ventured to study this enigmatic clinical entity in a tertiary care hospital, with a goal of understanding the patterns of disease distribution and the varied clinical and histopathological presentations.

REVIEW OF LITERATURE

Vasculitis is the inflammation of the vessel wall. It can affect small, medium and large vessels. The trigger for vasculitis may be primary (no known cause or association), secondary to infection, drug intake, connective tissue diseases or incidental (traumatic ulceration or diffuse neutrophilic infiltrates). Clinically, vasculitis can present with an array of manifestations which in turn depends upon the size of vessel involved. The most common of them are cutaneous such as palpable purpura, haemorrhagic vesicles, ulcers, urticaria, nodules, livedo, infarcts or digital gangrene. Histology of the lesions is necessary for a definitive diagnosis of vasculitis. Since both the clinical manifestations and histology may overlap between diseases, it is challenging to arrive at a diagnosis. Therefore, it must be correlated with clinical history, physical and laboratory findings.

HISTORY

The Latin word 'purpura' may have originated from the Greek 'porphyra', a colour produced by several species of sea snails in the family 'muciridae'[6]. Purpura was first used in association with infectious diseases such as hemorrhagic fevers.

Later, the English dermatologist, Robert William clearly differentiated purpura caused by systemic infections from non infectious cause [7,8]. He wrote elaborately about the condition on his masterwork on cutaneous diseases (1808) in which, descriptions of purpura associated with Henoch- schonlein can be recognised. He also explained about the predilection of purpura to lower extremities, its occurrence as groups of lesions and association with different systemic diseases.[8]

Johann Lukas Schönlein, his student Eduard Heinrich Henoch, and later William Osler, explained a broad spectrum of signs and symptoms that were associated with purpura and small-vessel vasculitis, such as arthritis, abdominal pain, peripheral neuropathy, pulmonary hemorrhage, and nephritis [9-12]. Osler recognized that these manifestations were caused by necrotizing inflammation in small vessels of the body [2].

The concept of purpura was related to leukocytoclastic vasculitis by Zeek et al in 1948 and 1952. They called this form of vasculitis affecting the small vessel as the hypersensitivity angiitis.[13,14]

In 1893, Henry Radcliff Crocker (1845-1909), an English dermatologist examined a six year old who presented with discrete, tender, purplish red nodules over the knees, buttock, fingers, and elbows. He named the condition erythema elevatum diutinum.[8] Later in 1929, Fred Weidman and John Besancon described the condition as a form of vasculitis. [15]

Adolf Kussmaul and Rudolf Maier in 1866, reported on a 27 year old patient who presented with fever, cough, weight loss, abdominal pain, paresthesias, polyneuropathy and proteinuria. They called the condition 'periarteritis nodosa', which was later named as polyarteritis nodosa. [16]

Friedrich Wohlwill in Germany, first described microscopic polyangiitis and distinguished it from polyarteritis nosoda. [17] Wegener's granulomatosis, which is a vasculitis of both small and medium vessels was first described by a medical student, Heinz Klinger. Later, it was Friedrich Wegener, a pathologist who observed in 11 patients array of manifestations such as sniffles , destructive lesions of the nose and throat, respiratory tract, spleen, and kidneys. He had no difficulty in identifying the pathologic changes as a mixture of vasculitis and granuloma formation. [18,19]

CLASSIFICATION

Classification of vasculitis has been one of the greatest challenges in medicine. Attempts to classify have been made from the mid 19 th century. In 1952, the classification put forth by Zeek based on the size of the vessel wall and histopathology has served as the basis for current understanding of vasculitis.[13,14] In 1952, Gilliam and Smiley proposed a revision of this classification. Thereafter a number of other systems have been proposed.[20]

Currently, the most widely adopted classification system is the of Chapel Hill Consensus Conference (CHCC), which is based on pathological criteria.[2] The other widely used system is the American College of Rheumatology (ACR), which is based predominantly on clinical findings.[21,22]

Classification of cutaneous vasculitis adapted from the 2012 Chapel Hill Consensus nomenclature [23]

Single organ (skin) small vessel vasculitis

- Cutaneous small-vessel vasculitis
- Urticarial vasculitis (excluding immune complex disease)
- Erythema elevatum diutinum

- Acute haemorrhagic oedema of infancy
- Recurrent cutaneous necrotizing eosinophilic vasculitis
- Granuloma faciale

Small vessel immune complex associated vasculitis

- IgA vasculitis (Henoch–Schönlein purpura)
- Cryoglobulinemic vasculitis
- Hypocomplementemic urticarial vasculitis (HUV)
- Anti Glomerular basement membrane vasculitis (anti-GBM/ Goodpasture syndrome)

Small vessel ANCA associated vasculitis

- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA/Wegener's granulomatosis- WG)
- Eosinophilic granulomatosis with polyangiitis (EGPA/Churg–Strauss syndrome)

Medium vessel vasculitis

- Polyarteritis nodosa (PAN)
- Kawasaki disease

Large vessel vasculitis

- Giant cell arteritis (GCA)
- Takayasu arteritis

Cutaneous vasculitis associated with systemic disease or variable vessel size

- Behçet syndrome
- Lupus vasculitis
- Sarcoid vasculitis
- Rheumatoid vasculitis

HISTOLOGY OF CUTANEOUS VASCULATURE

Arteries entering the skin form a ‘deep plexus’ between the subcutaneous tissue and the dermis. From this plexus, arises multiple vertically oriented reticular dermal vessels which unite to form the ‘superficial vascular plexus’ between the papillary and reticular dermis. This forms a layer of anastomosing arterioles and venules from which capillary loops emanate and extend into each dermal papilla with an ascending and descending limb and adnexal structure [24,25]. The epidermis is avascular.

The small arteries of deep plexus and arterioles of the dermis consists of three layers: an intima, composed of a single layer of endothelial cells and an internal elastic lamina, media which contains variable number of muscle layers and an adventitia made of connective tissue. The capillaries are composed of a layer of endothelial cells and incomplete layer of pericytes. A basement membrane is present peripheral to the endothelial cells and surrounds the pericytes. The veins have thinner walls and the above layers are less clearly defined. The postcapillary venules resemble capillaries but the former have more than one layer of pericyte.[26]

Arterioles and venous segments can be differentiated on the basis of basement membrane. The veins have multi laminated basement membrane whereas, the arterioles possess a homogenous appearance. Another feature is the presence of elastin and smooth muscle cells in the walls of arterioles which is absent in the venules.

Ultrastructurally, endothelial cells possess many cellular organelles, including smooth and rough endoplasmic reticulum, mitochondria, lysosomes and many pinocytic vesicles. Weibel-palade bodies are endothelium-specific inclusions, which are electron dense,

rod shaped cytoplasmic organelles containing factor XIII-related antigen, von willebrand factor and GMP-140.

A number of endothelial-specific antigens have been recognised. Endothelial cells are major source of angiotensin converting enzyme, various cytokines, adhesion molecules and enzymes involved in processes like endocytosis and vesicular transport. Acid phosphatase has been localised to the endothelium and staining for the same demonstrates the capillary loop in each dermal papillae.

HISTOPATHOLOGICAL FEATURES OF VASCULITIS

Inflammation of the vessel wall leads to some characteristic changes which are essential for the diagnosis of vasculitis:

a) Inflammatory cell infiltrate
b) Evidence of vascular injury.

The density of cells and type of inflammatory cells present depends upon the stage and nature of disease process.

The cellular infiltrate predominates within the dermal vessels, blurring the vascular outlines. Karyorrhectic nuclear debris, or nuclear

dust gives the infiltrates a dirty appearance. In the early stages, neutrophils/ eosinophils predominate and in the late stages, there is an excess of lymphocytes and macrophages. Inflammatory cells may also be scattered throughout the upper dermis within and around the collagen bundles. [27]

Evidence of vessel destruction include endothelial necrosis and deposition of fibrinoid material in the lumen or vessel wall. The fibrinoid material is due to the accumulation of plasma proteins including coagulation factors in the vessel wall that are later converted to fibrin. These changes commonly coexist with other evidences of vascular injury such as edema and extravasation of erythrocytes.They are not specific for vasculitis and are also seen in vaso occlusive disorders. Edema together with fibrinoid necrosis gives an 'smudgy appearance' to the vessel wall.

DIRECT IMMUNOFLUORESCENCE STUDIES :

The type and pattern of deposits in immunofluorescence\nce is of diagnostic help in evaluation of vasculitis.

1) Deposition of C3, IgM, IgA and IgG in and around the vessels is the feature of immune complex vasculitis - most cases of cutaneous vasculitis and LCV. [27,28,29]

2) Predominant IgA deposition - HSP vasculitis

3) Basement membrane zone and keratinocyte nuclear immunoreactants with predominant Ig G - Connective tissue disease vasculitis, lupus vasculitis

4) Clinical picture of urticarial vasculitis with a basement zone immunoreactants - Hypocomplementemic UV in association with CTD.

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY TESTING :

ANCA are mostly IgG antibodies directed against the components of primary granules of neutrophils and lysosomes of monocytes[30] .They translocate to the cell's surface on activation by cytokines such as TNF alpha. The antibodies bind to the surface antigens leading to enhanced adhesion of neutrophils to the vascular endothelium. The release of inflammatory mediators lead to vascular damage and recruitment of additional inflammatory mediators.

By immunofluorescent staining, there are two patterns observed:

(1) cytoplasmic (c)-ANCA – antibodies directed against the antigen proteinase 3 (PR3); and

(2) perinuclear (p)-ANCA – antibodies directed against the antigen myeloperoxidase (MPO) and some other antigens such as lactoferrin, cathepsin G and elastase.

ANCA testing is a useful adjuvant in the evaluation of vasculitis. ANCA-associated vasculitides are

1. Granulomatosis with polyangiitis
2. Microscopic polyangiitis
3. Eosinophilic Granulomatosis with polyangiitis.

c ANCA is positive in 90% of cases of GPA and 30% of MPA. pANCA is positive in 60% of patients with MPA and EGPA [31] . It is also found to be positive in drug-induced vasculitis, connective tissue disorders, inflammatory bowel diseases, other chronic inflammatory states and certain malignancies. In order to increase the specificity of ANCA testing, the indirect immunofluorescence

testing done to detect the pattern of ANCA is followed by ELISA that specifically detects antibodies against MPO and PR3.

INDIVIDUAL VASCULITIS

CUTANEOUS SMALL VESSEL VASCULITIS (CSVV)

Cutaneous small vessel vasculitis affects the skin by producing leukocytoclastic angiitis of cutaneous vasculature. It is also termed as allergic cutaneous vasculitis or hypersensitivity vasculitis. It is a disease that predominantly localised to the skin.

Epidemiology

The annual incidence of CSVV is between 15 and 30 per million. The mean age of onset is between 36 and 56 years. [26]

Criteria for diagnosis :

The presence of three of the following five criteria have 84% specificity for CSVV:

(i) age of onset greater than 16 years ;

(ii) history of drug intake prior to disease onset ;

(iii) the presence of palpable purpura;

(iv) the presence of a maculopapular rash; and

(v) a biopsy demonstrating granulocytes around an arteriole or venule [32] .

Predisposing factors :

There are many causes of cutaneous vasculitis, but most CSVV are idiopathic[33] . Bacterial cause has been implicated. There are also multiple other factors thought to contribute to CSVV, which are listed below.

- Food allergies
- Ant bite
- Exercise
- Solid organ malignancies

Drugs :

- Acenocoumarol
- Propylthiouracil
- Ibuprofen
- Methotrexate
- Warfarin, Coumarin
- Procainamide

- Infliximab
- Interferon 1B
- Granulocyte colony-stimulating factor
- Omeprazole
- Insulin
- Imipenem-cilastatin
- Gabapentin,lamotrigine

The major skin manifestation of CSVV is palpable purpura over the extremities. It is usually asymptomatic. It may progress to form papules, pustules, nodules, vesicles or bullae that can necrose, ulcerate and form post inflammatory pigmentation. The lesions occur in crops resulting from exposure to the inciting stimulus and the risk factors to predict relapse are not known. The lesions resolve with leave hyperpigmentation and hemosiderosis that take weeks or a few months to resolve. It is a diagnosis of exclusion after doing a prompt search for wide array of diseases that present in a similar way.

Histology shows leukocytoclastic vasculitis. In superficial dermal vessels, IgM / C3 get deposited in up to 80% of fresh lesions[27] .

ERYTHEMA ELEVATUM DIUTINUM (EED)

Erythema elevatum diutinum is rare disease occurring in adults in the fourth to seventh decade. It was first described by Hutchinson and Burry. Few diseases seen in association with EED are some autoimmune diseases like rheumatoid arthritis, IBD, HIV, gammaglobulinemia, multiple myeloma and type 1 diabetes [34,35] . Among these, it is strongly associated with hematological malignancies and EED lesions precede it by several years [36] . EED is characterised by symmetrical violaceous to red brown papules, plaques and nodules which are soft in the early stages and undergoes fibrosis and atrophy in late stages. It is commonly seen over the dorsa of the hands, knees and buttock.

Histology shows leukocytoclastic vasculitis with little fibrin deposition with or without eosinophils in the upper and mid dermis. Late lesions demonstrate angiocentric eosinophilic fibrosis and endothelial proliferation. Along with it, cholesterol deposits in histiocytes can be seen, termed as 'cholesterolosis'. Histopathology of dermal nodules show spindle cells and fibrosis [37,38] . Histological differentials include cutaneous small vessel vasculitis, Sweet's syndrome and granuloma faciale.

Serum levels of Ig A is increased and Ig A ANCA can be positive in 60% of cases [39] .

GRANULOMA FACIALE :

Granuloma faciale, also called 'Eosinophilic granuloma', is an uncommon condition occurring between 40 and 60 years of age. It is localised vasculitis confined to the skin. It is characterised by asymptomatic soft reddish brown cutaneous nodules over the face, associated with telangiectasia[40] . The surface is smooth and shows prominent follicular orifices and mild scaling. The lesions do not ulcerate.

Histology shows rich eosinophilic and plasma cell infiltrate in the upper dermis along with LCV [41] . There is never a granuloma found[42] . A band of normal collagen free of infiltrate separates the epidermis from the infiltrates of dermis called the 'Grenz zone'.

Clinical variants are extra facial granuloma faciale and eosinophilic angiocentric fibrosis. The latter is considered a mucosal variant of granuloma faciale. It occurs in the nasal passages and upper airways along with the skin lesions of granuloma faciale.

Ig A VASCULITIS / HENOCH- SCHONLEIN PURPURA (HSP)

Ig A vasculitis is an immune complex vasculitis with predominant **Ig A1** immune deposits in the small vessels. It affects both children and adults, with a peak incidence of 4-6 years in children. Incidence appears to be more in winter, spring and autumn. Respiratory infections, commonly with streptococcus, may be a precursor in a small number of cases[43,44] . The other bacteria that are implicated are Bartonella and Hemophilus.

The characteristic feature of HSP is the increased serum levels of of IgA and immune complexes containing IgA. There are 2 subclasses of IgA - IgA1 and IgA2. The hinge region of IgA1 is highly glycosylated in normal individuals [45] . This is highly essential for the normal clearing of these molecules. Defective glycosylation in patients with HSP results in decreased elimination of IgA1 molecules. It also exposes certain antigens (GalNAC in terminal glycan). As a result of this, exposure to certain microorganisms that also express GalNAC containing sugars result in production of antibodies that cross react with IgA1 molecules forming immune complexes. This explains the possible association with respiratory illness precipitating HSP.

The classical findings include purpura, arthritis and abdominal pain. The purpura typically affects extensor aspects of limbs and buttocks in a symmetrical fashion. Retiform pattern is characteristic. Urticaria, vesicles, bullae and ulcers can also occur. Renal involvement in the form of proteinuria and haematuria occurs in 40-50%. It is less common in children. Gastrointestinal (GI) involvement occurs in 65%, with frank GI bleeding in 30 percent. Arthritis, non erosive type occurs in 75% of individuals[46] .

Histology shows LCV with predominant IgA deposits in direct immunofluorescence. No laboratory test is specific for HSP.

Prognosis - Relapse is seen in 25% of patients and it is usually mild. It becomes chronic in 5%. End stage renal failure occurs in 1-3%.

Differential diagnosis includes IgA nephropathy, Idiopathic thrombocytopenic purpura, septic shock, SLE etc,.

CRYOGLOBULINEMIC VASCULITIS

Cryoglobulinemic vasculitis is a small vessel vasculitis affecting skin, joints, nerves and kidneys. Cryoglobulins are abnormal immunoglobulins that precipitate at temperatures lower than the body temperature. The vasculitis is due to the cryoglobulins that are deposited as immune complexes. There are three types of cryoglobulins:

1. Monoclonal Ig - either Ig G / Ig M - seen in 25% of cases. Associated with multiple myeloma / Waldenstrom's macroglobulinemia

2. Monoclonal IgM + mixed polyclonal IgG- seen in 25%

3. Polyclonal IgM (with rheumatoid factor activity)+ Polyclonal IgG - seen in 50-60% of cases.

Type II and III cryoglobulinemia manifest as vasculitis. Most common cause of Type II and III cryoglobulinemia is Hepatitis C virus (in 80% of cases) [47] . Not all patients with Hepatitis C and cryoglobulins develop vasculitis. Therefore there may be a different mechanism responsible for the development of disease

manifestations. There is a significant low level of circulating regulatory T cells in patients with manifestations compared to those with just cryoglobulinemia.

Other causes include autoimmune diseases such as Sjogren's disease, lymphoproliferative diseases and other viral infections.

The classic Meltzer's triad of arthralgia, purpura and weakness that was once described in CV is found to be present only in 30% of cases [48] . Clinical manifestations include palpable purpura, sensorimotor neuropathy, mononeuritis multiplex, membranoproliferative glomerulonephritis with nephrotic range proteinuria [49] . In associated connective tissue disease, Raynaud's phenomenon may be seen. Cold and immobility can precipitate an acute episode.

Histology reveals pandermal LCV which may extend into the subcutis. Immune complex deposits are seen as eosinophilic PAS positive deposits in the vessel wall. Chronic lesions show mononuclear predominant infiltrate. Vasculitic changes in other organs such as kidney, lung and vasa nervosa are also observed. There is a low complement C4 and a normal C3 in the blood in all cases. The gold standard for diagnosis is the demonstration of

cryocrit. Care should be taken in transporting the blood to the laboratory at 37 degree celsius.

URTICARIAL VASCULITIS (UV) :

Urticarial vasculitis also called MacDuffie syndrome is characterised by persistent weals with histopathology showing leukocytoclastic vasculitis. Five to ten percent of chronic urticaria patients were found to have urticarial vasculitis[50] . There are two types of UV- Normocomplementemic and hypocomplementemic UV. Normocomplementemic type accounts for 70-80% of UV and runs a benign course.

Hypocomplementemic UV has a chronic relapsing course with urticaria, hypocomplementemia and anti-C1q antibodies. The peak incidence is between third and fifth decade and it occurs exclusively in women[51]. It is often idiopathic but it can be associated with connective tissue disease such as SLE, sjogren's and sometimes infections and haematological malignancies[51]. Cutaneous lesions of both the forms of UV are weals persisting for more than 24 hours. They tend to be more painful than pruritic and heal with discolouration. Angioedema may occur, as may purpura, livedo reticularis, bullae and nodules. It is also associated with other

systemic features such as arthritis, glomerulonephritis, chronic obstructive pulmonary disease, ophthalmic complications and abdominal pain.

The sera of the patients have polyclonal IgG directed against collagen like region of C1q, leading to decrease in C1q , activation of complement pathway and formation of weals[52]. Skin biopsy shows minimum of leukocytoclasia with or without fibrinoid deposits.

ANTI - GLOMERULAR BASEMENT MEMBRANE VASCULITIS (Anti-GBM vasculitis**):**

Anti-GBM vasculitis, also called the Goodpasture syndrome, involves the capillaries of glomeruli and lungs. Cutaneous involvement with vasculitic changes is uncommon. Peak incidence occurs between the third and seventh decade.

Autoantibodies are directed against NC1 domain of α chain of Type IV collagen [53]. This molecule is found in the lung and kidney. The immune complexes get deposited in the basement membrane zone of lung, kidney and rarely the skin. [54]

Clinical features include cough, hemoptysis, fatigue and breathlessness. These symptoms precede renal involvement. Skin involvement includes erythematous macules over the instep of the foot. The survival depends on the early renal function. Death occurs early if untreated.

Small vessel ANCA associated vasculitis

MICROSCOPIC POLYANGIITIS (MPA)

Microscopic polyangiitis is a necrotising, non granulomatous[23] inflammation affecting mainly the small vessels. The peak age of incidence is between 64 and 75 years of age.

Anti Neutrophilic cytoplasmic antibodies causes degranulation of TNF primed neutrophils. The degranulation of neutrophils cause respiratory burst and release of toxic oxygen radicals and ultimately to vascular inflammation [55] .

MPA initially presents with constitutional symptoms, such as arthralgia, fever and weight loss several weeks before the onset of other symptoms. Skin lesions as an initial presentation occurs in about 40 percent of cases[56]. They are palpable purpura, livedo reticularis, splinter haemorrhages and ulcers. Other systems involved

are the renal and lung leading to necrotising crescentic glomerulonephritis (without immune complex deposition) and pulmonary hemorrhage respectively. Neurologic involvement present as peripheral neuropathy or mononeuritis multiplex in about one third of patients. There is also an increased risk of coronary artery disease and hypertension which leads to raised incidence of myocardial infarction and cerebrovascular accidents [57] .

Histopathology shows segmental necrotising vasculitis around small blood vessels. There is no granulomatous inflammation. Blood investigations show anemia of chronic disease and increases levels of acute phase reactants. There is also hematuria and proteinuria present. ANCA against MPO or PR3 is present in almost all the patients. Imaging helps to find out involvement of lungs. The criteria to diagnose and differentiate from other ANCA positive vasculitis is the lack of biopsy or other surrogate markers of granulomatous inflammation.

GRANULOMATOSIS WITH POLYANGIITIS / WEGENER'S GRANULOMATOSIS :

Granulomatosis with polyangiitis is characterised by necrotising granulomatous inflammation of small and medium

arteries, upper and lower respiratory tract. Friedrich Wegener first described three cases who presented with high grade fever and negative for septic screening, raises ESR, nasal septal involvement and eventually died. The term 'Wegener's granulomatosis' was first used by Sven Johnsson [58] . At the international consensus,2013, the name was changed to Granulomatosis with polyangiitis. ANCA induced neutrophil degranulation and release of oxygen radicals leads to vascular inflammation. Bacteria may play a role in the pathogenesis. Staphylococcus aureus is the one implicated. It plays a role in the formation of granulomas which occurs prior to the onset of vasculitis. The granulomas composed predominantly of granulocytes act as the source of proteinase 3 (PR3) that helps to continue the inflammatory process.

The peak age of onset is 45-65 years. It is also common in children, the median age of onset being 14 years [59,60]. They commonly present with upper and lower respiratory tract symptoms like sinusitis, epistaxis, rhinorrhoea, otitis, hemoptysis and cavitating nodules in the lungs. Mucocutaneous involvement occurs 40% of the cases. Skin lesions include palpable purpura, subcutaneous nodules, vesicles and large pyoderma gangrenosum like ulcers. The common

mucosal lesion is oral ulcers and strawberry gingiva. Renal involvement occurs in about 18% and eventually leads to glomerulonephritis in 77%.

Biopsy showing LCV and granulomatous inflammation is found in 50% of the specimens. cANCA is positive in 60-90% of cases and pANCA in 10 percent.

Patients when untreated have a 1 year mortality rate of 80%[61]. Cancer risk is increased two fold (acute myeloid leukemia and bladder cancer) [62,63]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Eosinophilic granulomatosis with polyangiitis also called the Churg- strauss syndrome is characterised by eosinophil-rich necrotising granulomatous inflammation vasculitis and respiratory involvement. The peak incidence occurs at the age of 50. The clinical presentation is divided into three phases.

1. The first phase consists of adult onset asthma, allergic rhinitis and nasal polyps.

2. The second phase is that of peripheral and tissue eosinophilia.

3. The third phase consists of vasculitic phase involving all the organ systems. Cutaneous manifestations are most common in this phase.

Cardiomyopathy, mononeuritis multiplex, diffuse alveolar hemorrhage, glomerulonephritis can occur. The leading cause of death is due to the cardiac involvement which occurs in about half of the patients.

Histology shows eosinophilic infiltration with extravascular granulomas and necrotising vasculitis of small and medium sized arteries. Only about 30% of patients show P-ANCA or C-ANCA positivity.[64]

Medium vessel vasculitis

POLYARTERITIS NODOSA

Polyarteritis nodosa also called the kussmaul Maeir disease is a rare necrotising arteritis of medium and small arteries and spares the small vessels. The disease that is limited to the skin is called the cutaneous PAN[65]. The peak age of incidence is 60 years. It can be associated with Hepatitis B infection[66], streptococcal infections,

inflammatory bowel disorders and malignancies. Systemic PAN presents with fever, arthralgia, weight loss, paresthesias, abdominal pain and shortness of breath. Bad prognostic factors are cardiac failure and mesenteric ischemia[67]. Skin involvement in systemic PAN occurs in about 25 percent. Palpable purpura, subcutaneous nodules, livedo reticularis and gangrene of the digits are some of the skin manifestations.

Histology findings are LCV with lymphocytic infiltrates of the medium sized arteries of the subcutaneous tissue[68] . The vessels show target like appearance caused by the eosinophilic ring of fibrinoid necrosis. Systemic PAN is always negative for ANCA. It is positive in around 10-25% of cutaneous PAN.

KAWASAKI DISEASE

Kawasaki disease also called the mucocutaneous lymph node syndrome affects medium and small sized arteries. It is most common among infants and young children less than five years of age. The first phase is an acute febrile illness accompanied by acral edema, conjunctivitis, strawberry tongue and lymphadenopathy, lasting for about 2 weeks. The following phase lasts for about 3 weeks and carries the highest risk for coronary artery involvement, leading to

death from aneurysms and myocardial infarctions. The convalescent phase is characterised by returning of ESR and C- Reactive protein to normal levels. This takes a period of about 3 weeks.

LARGE VESSEL VASCULITIS

Large vessel vasculitis includes Giant cell arteritis (GCA) and Takayasu arteritis. GCA is a granulomatous arteritis affecting aorta and its major branches and commonly the temporal arteries, presenting with tender palpable arteries, headache, claudication of jaw muscles and loss of vision. Rarely, GCA may present with skin infarction. [69]

Takayasu arteritis/ pulseless disease also affects the aorta and its major branches. Skin manifestations include subcutaneous nodules, erythema nodosum, erythema induratum and pyoderma gangrenosum like ulceration. [70]

DRUG INDUCED VASCULITIS :

Drug induced vasculitis, one of the secondary causes of vasculitis accounts for 3% of vasculitis [71] . It is associated with almost every class of drug. Small vessel vasculitis with cutaneous manifestations occurs in the majority of cases, although medium

vessel vasculitis can also occur. Commonly implicated drugs are antibacterials, analgesics, antiviral, anticonvulsants, antipsychotics, anticoagulants etc,.

Cell mediated and humoral mediated immunity are both believed to play important role. The most probable pathogenetic mechanism is the activation of neutrophils, T cells and endothelial cells by antineutrophil cytoplasmic antibodies (mostly pANCA) [72] . The cause-effect relationship between ANCA and drug induced vasculitis seems to be most applicable for the drugs propylthiouracil and hydralazine [73].

The clinical manifestation of drug induced vasculitis is indistinguishable from primary vasculitis. It occurs after a mean period of 1-3 weeks after drug exposure [74] . Systemic manifestation such as fever, arthralgia, renal and lung involvement can also occur.

No specific laboratory or histological feature is specific for the diagnosis. Eosinophilia is seen in 25% of cases of localised cutaneous involvement and in 80% of cases of systemic involvement. Biopsy to confirm vasculitis, ANCA levels, arteriogram can be done.

CONNECTIVE TISSUE DISEASE VASCULITIS:

Connective tissue disease (CTD) vasculitis is suspected when patients with histology proven vasculitis also have associated symptoms such as dry eyes and mouth, photosensitivity, arthritis, sclerosis of skin and serological evidence of antibodies such as ANA, RF, APLA, anti - DNA and anti - Ro, La [27].

The presentation is usually widespread with involvement of multiple organs in addition to the small and medium vessel vasculitis. Involvement of arterioles and postcapillary venules is characteristic. The diagnosis is supported by extravascular histological features of skin, kidney etc,.

INFECTIVE VASCULITIS :

Infective vasculitis can be caused by all types of infections - viruses, bacteria, fungi, protozoa and helminths. The term 'Septic vasculitis' is used to describe infective vasculitis caused by septicemia and infective endocarditis [27].

Histology reveals the following features -

- small vessel neutrophilic vasculitis
- scaty perivascular fibrin / fibrin thrombi

- less eosinophils and lymphocytes compared to primary vasculitis or drug induced vasculitis.

There may be associated subcorneal, intraepidermal or subepidermal neutrophilic collection along with tissue eosinophilia to support the diagnosis.

MIMICKERS OF CUTANEOUS VASCULITIS (PSEUDOVASCULITIS)

1) Haemorrhage

Pigmented purpuric dermatitis

Idiopathic thrombocytopenic purpura

2) Embolism

Atrial myxoma

Cholesterol embolus

3) Thrombosis

Antiphospholipid antibody syndrome (APS)

Thrombotic thrombocytopenic purpura

Purpura fulminans

4) Vessel wall defect

Calciphylaxis

Amyloidosis

AIMS AND OBJECTIVES

To study the epidemiological spectrum of cutaneous vasculitides as seen in a dermatologic clinic and to determine the clinico-pathological correlation.

MATERIALS AND METHODS

STUDY DESIGN

Cross-sectional observational study.

STUDY AREA

Coimbatore Medical College and Hospital, Coimbatore - Department of Dermatology, Venereology and Leprosy

STUDY POPULATION

Patients attending outpatient clinic of Department of Dermatology, CMCH, Coimbatore.

STUDY PERIOD

Twelve months - June 2016 to May 2017

SAMPLE SIZE :

Forty (40) consecutive patients who presented with palpable purpura, papules, plaques, nodules, vesicles, bullae, weals or other features suggestive of vasculitis were included in the study. All the patients were explained about the study and an informed consent was obtained from all the patients in the language of their convenience - Tamil / English.

SAMPLE DESIGN :

The sample was designed according to the below mentioned inclusion and exclusion criteria.

INCLUSION CRITERIA:

All patients with clinical evidence of cutaneous vasculitis

a. simultaneous crops of palpable purpura,

b. papules, plaques, nodules, vesicles, bullae, pustules, ulcers and

c. other cutaneous findings like urticaria, livedo reticularis or edema

EXCLUSION CRITERIA:

a) patients with thrombocytopenia (<50, 000/mm^3)

b) disorders of coagulation;

c) patients on warfarin/heparin

STUDY DESIGN :

In all patients presenting with features suggestive of vasculitis, a thorough clinical history regarding age, sex, duration of the disease, presence of other associated symptoms, history of intake

of any medications was taken. Any significant past illnesses and comorbid conditions was recorded.

Clinical examination to rule out systemic involvement was done. Blood counts, bleeding and clotting time, renal and liver functions tests, chest radiographs, urine examination, ASO, CRP, RF, screening for infections such as hepatitis C & B and relevant autoantibodies such as ANA and ANCA were done depending on history and examination findings . Patients were then selected for study based on the inclusion and exclusion criteria. An attempt was made to give a diagnosis based on the clinical findings.

Biopsy from the lesion that is less than 48 hours duration was taken from all the patients. A standard 4mm disposable punch was used to take biopsy from the suspected lesion. The biopsy specimen was sent for both routine histopathological examination (Hematoxylin and eosin) and direct immunofluorescence. The results were first interpreted by senior pathologists. In every case the pathologic diagnosis was reconfirmed by the investigator. All of the above investigations were done on the first visit or in the subsequent visits to the hospital.

The histopathological findings observed were broadly classified into 3 main types.

- Leukocytoclastic vasculitis :

Characterised by fibrin deposition in the vessel wall along with neutrophilic infiltration. In addition to the above, there may associated endothelial swelling / disruption and extravasation of RBC's.

- Lymphocytic vasculitis :

Presence of lymphocytic cuff around the blood vessels.

- Granulomatous vasculitis :

Characterised by palisading neutrophilic granulomas around blood vessels.

The clinical presentations were correlated with a relevant work up and a diagnosis was arrived at based on the Chapel Hill consensus nomenclature for cutaneous vasculitis- 2012.

OBSERVATION AND RESULTS

40 patients were enrolled into the study.

1.Age Distribution

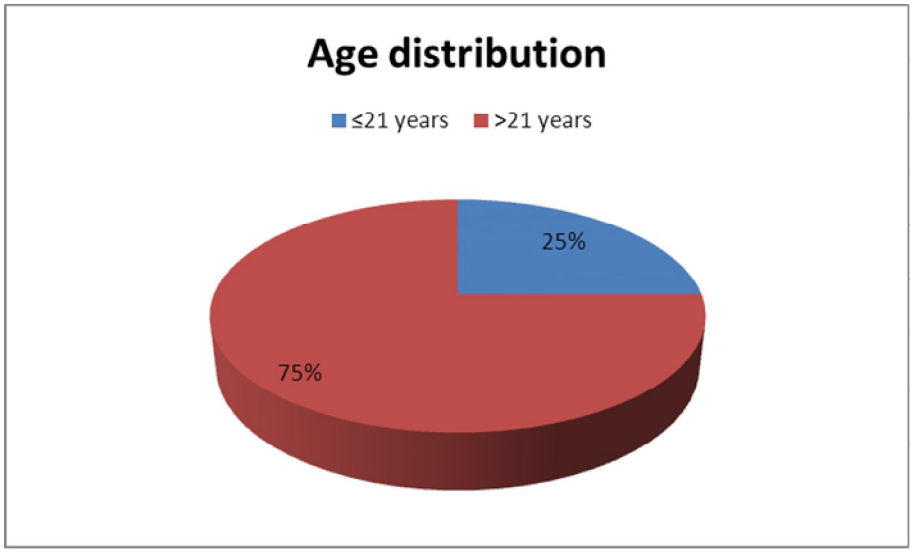
A total of 40 patients were included in the study.

The mean age was 33 years (range - 11 to 68 years).

Table 1: Distribution of patients according to age

Age	n=40	Percentage
≤21 years	10	25%
>21 years	30	75%

Chart 1: Age distribution of patients.



2. Gender distribution

Males

Number of patients = 24 (60%)

Mean age = 34.95

Range = 15 to 68

Females

Number of patients = 16 (40%)

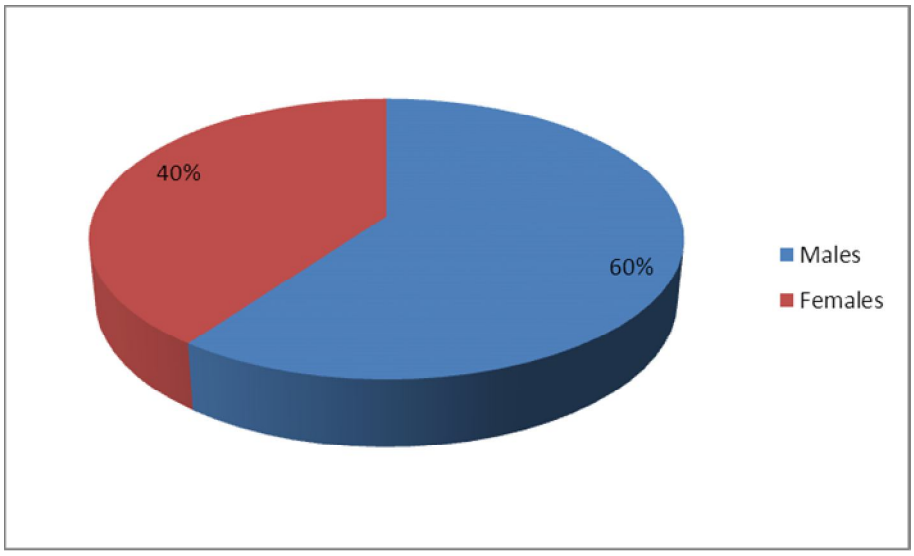
Mean age = 30.06

Range = 11 to 50

Table 2: Gender distribution of the patients

Sex	n=40	Percentage
Males	24	60%
Females	16	40%

Chart 2: Gender distribution of the patients



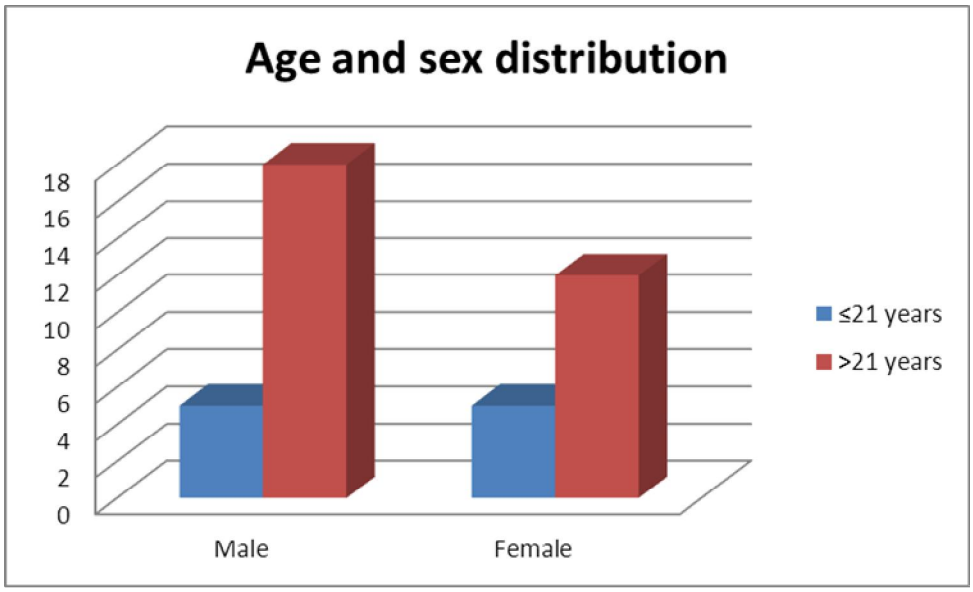
3. Age and Sex distribution

The age and sex distribution of patients is depicted below.

Table 3: Distribution of males and females between the two age groups (≤21 and >21 years)

Age	Male	Female
≤30 years	5 (12.5%)	5 (12.5%)
>30 years	18 (45%)	12 (30%)

Chart 3: Distribution of males and females between the two age groups (≤21 and >21 years)



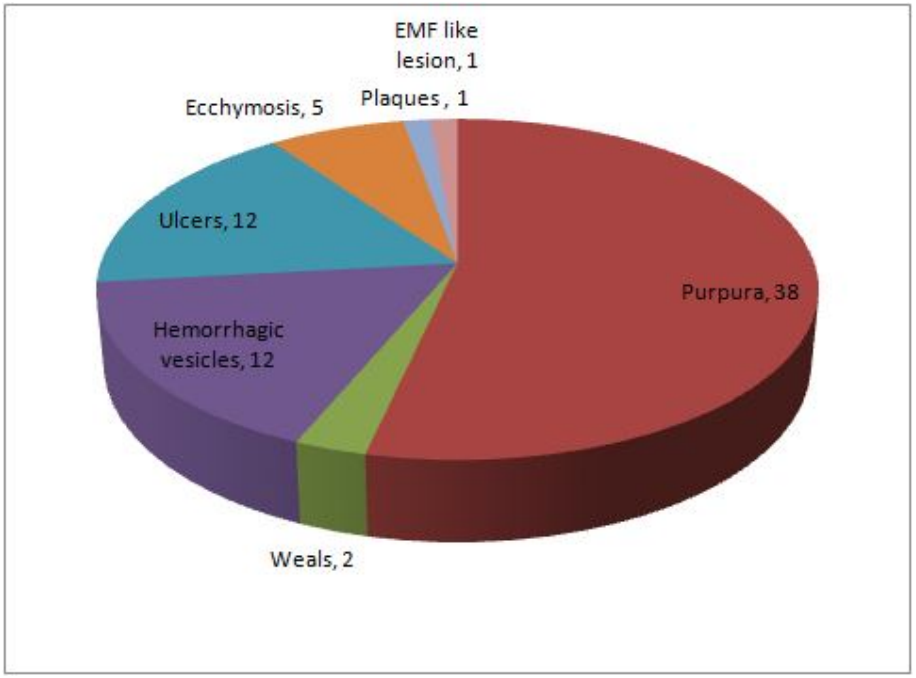
4. Types of skin lesions

The various skin lesions observed in the 40 patients were palpable purpura, weals, confluent purpura, hemorrhagic vesicles and ulcers. Many patients had more than one skin lesions.

Table 4: Frequency of various cutaneous lesions

Lesion	n=40	Percentage
Palpable purpura	38	95%
Weals	2	5%
Hemorrhagic vesicles	12	30%
Ulcers	12	30%
confluent purpura	5	12.5%
Plaques	1	2.5%
EMF like lesion	1	2.5%

Chart 4 : Frequency of various cutaneous lesions.



5. Systemic manifestations

Few of the patients presented along with systemic symptoms such as fever, arthralgia, abdominal pain, etc.

Table 5 : Frequency of systemic manifestations

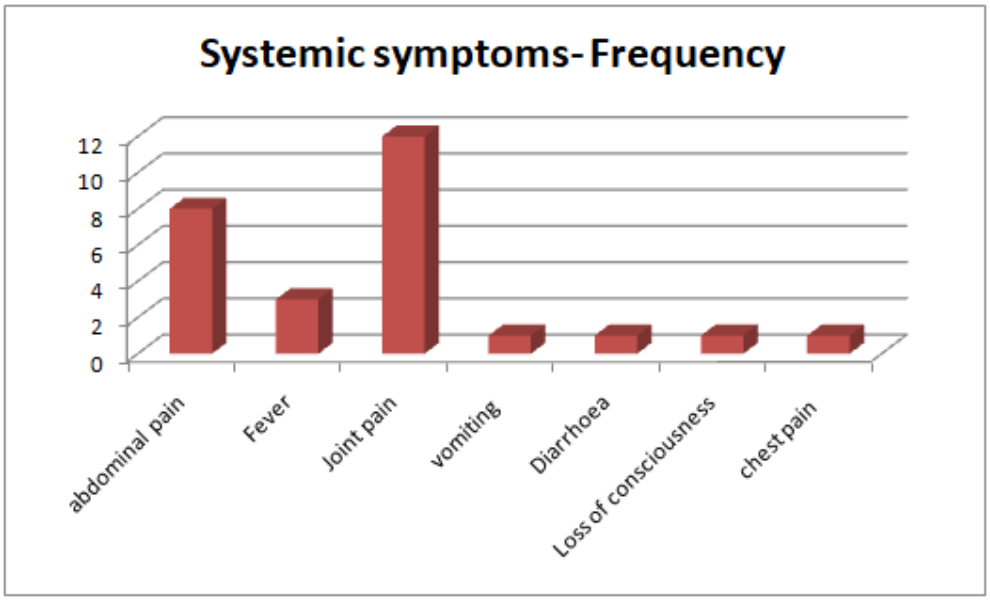
Systemic symptoms	n= 40	Percentage
Present	19	47.5%
Absent	21	52.5%

The various systemic manifestations that were seen in our study were fever, arthralgia, abdominal pain etc.

Table 6 : Frequency of systemic symptoms .

Symptoms	Frequency, n=40	Percentage %
Abdominal pain	8	20
Fever	3	7.5
Joint pain	12	30
vomiting	1	2.5
Diarrhoea	1	2.5
Loss of consciousness	1	2.5
chest pain with breathlessness	1	2.5
Loss of weight	1	2.5

Chart 5 : Frequency of systemic symptoms .



The most common systemic symptom associated was arthralgia (30%) followed by abdominal pain (20%). Knee joint was the most common joint involved (8 out of 12 patients). Vomiting, diarrhoea, loss of consciousness and chest pain with breathlessness was found in one patient each. The patient with chest pain and breathlessness had associated significant loss of weight.

6. Drug history

Sixteen (16) patients gave history of intake of drugs for illnesses that had occurred prior to the onset of vasculitic lesions. Few patients had consumed more than one drug.

Table 7 : Drug intake prior to the onset the skin lesions

Drugs	n=16 out of 40
Antibiotics	5
Analgesic	3
steroids	2
oral hypoglycemics	3
others	4
Unknown	2

The commonly consumed drugs were antibiotics in five, analgesics in three and oral hypoglycemics in three patients. Antihistamines, Tamoxifen, ATT and Thyroxine in one patient each. Two patients were taking drugs, the details of which were unknown. One of them was taking drugs for the treatment of infertility.

Chart 6 : Drugs taken prior to the onset the skin lesions

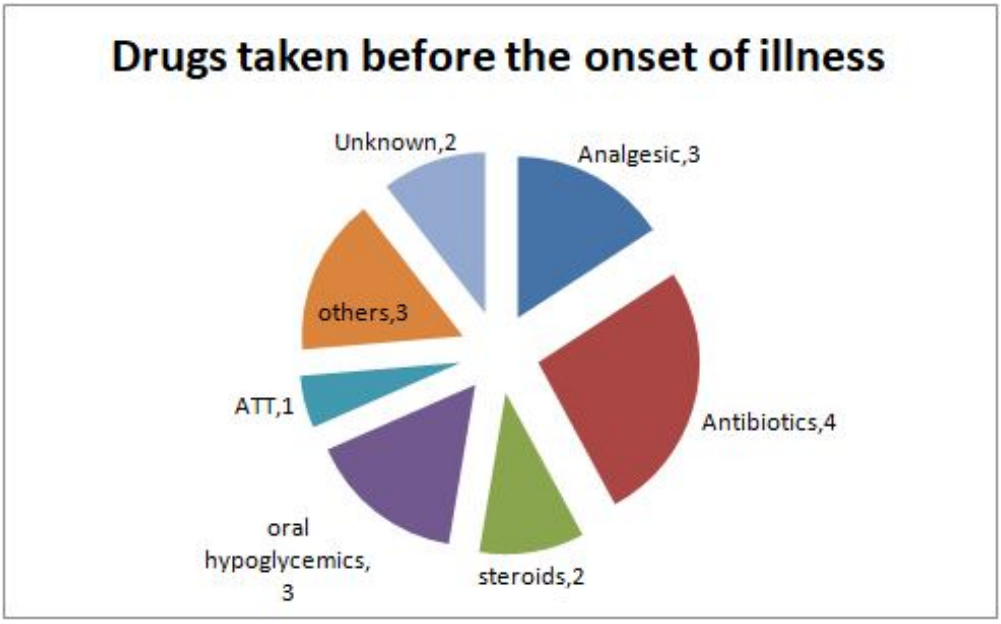


Table 8 : The details of the individual drugs consumed

Group	Drug	Number of cases
Antibiotics	cephalosporins	2
	Azithromycin	1
	Amoxicillin	1
	Ofloxicilin	1
Analgesics	Paracetamol	2
	Ibuprofen	1
Oral hypoglycemics	Metformin	2
	Glimepiride	1

The most common antibiotic consumed was cephalosporins. Azithromycin, amoxicillin and ofloxacin were consumed by one patient each. The most common analgesic consumed was paracetamol and the most common oral hypoglycemic was metformin.

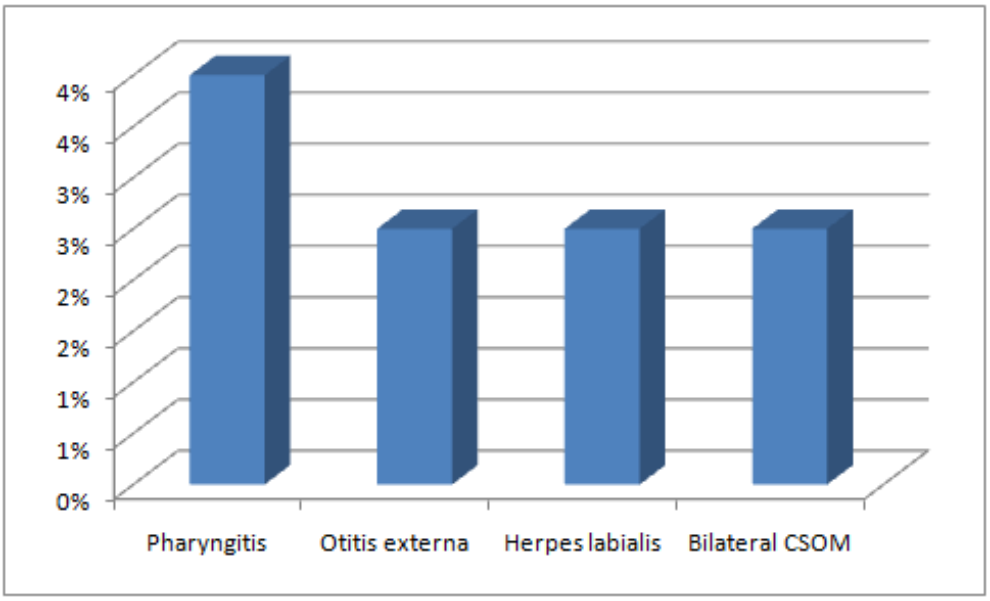
7. History of recent illness

History of infectious illness in the recent past (within a period of one month) was seen in 5 patients.

Table 9 : Frequency of recent infections

Infection	n=5 out of 40	Percentage
Pharyngitis	2	4%
Otitis externa	1	2.5%
Herpes labialis	1	2.5%
Bilateral CSOM	1	2.5%

Chart 7 : Frequency of recent infections

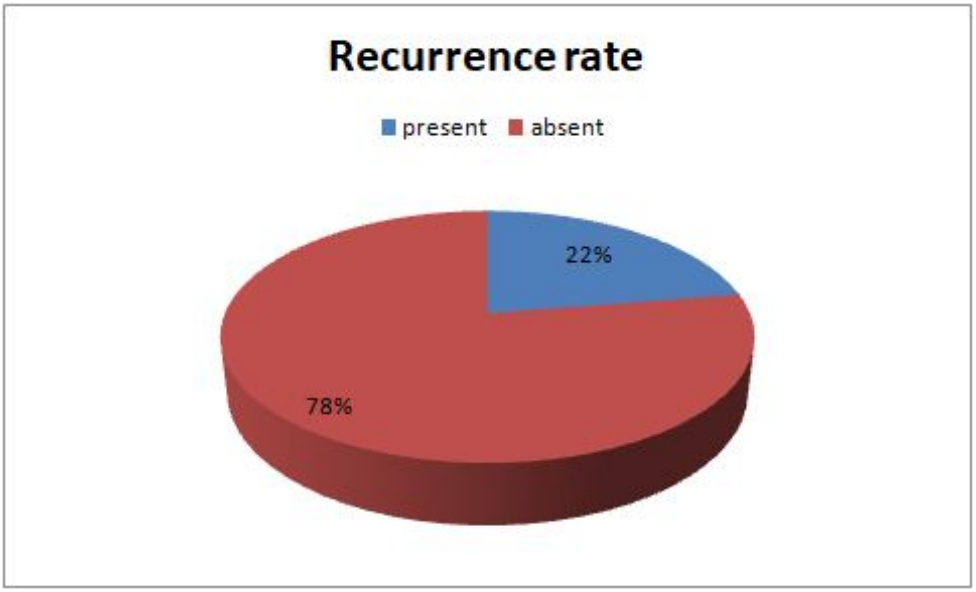


Two individuals suffered from pharyngitis just a few days prior to the onset of vasculitis. One patient presented with bilateral chronic suppurative otitis media (CSOM) along with bilateral facial palsy. All the above mentioned patients had also consumed drugs as a treatment of the infection except the one with herpes labialis.

8. Recurrence

Of the 40 patients, nine (9) patients had past history of similar illness.

Chart 8 : Rate of recurrence



9. Associations

Eight (8) out of forty patients had an associated non infectious medical illness. The relevance of the illness to the vasculitic lesions were not known except for one patient with bilateral CSOM who was later diagnosed as a case of Wegener's granulomatosis

1. Bullous pemphigoid
2. Hypothyroidism
3. Carcinoma of Breast
4. Polycystic ovarian disease
5. Atopy
6. Peripheral sensory neuropathy
7. Hiatus hernia
8. Bilateral facial palsy

The above illnesses had occurred in one patient each. All the seven patients were also on medications for their respective illnesses.

10. Laboratory parameters

The following blood investigations were done in all the 40 patients.

1. Complete blood count (CBC)
2. Renal function test (RFT)
3. Liver function test (LFT)
4. Urine routine
5. CRP
6. Infection screen (ASO titre, Hepatitis B & C and HIV)

Autoantibodies (RF, ANA, pANCA, c ANCA and Complement levels) were tested in only a few relevant patients.

7. Imaging – Chest X-ray and USG abdomen was done in all patients.
8. Other additional relevant investigations were done on individual patients.

Table 10 : Hematological workup and imaging

Abnormality	n=40	Percentage %
Leukocytosis	5	12.5
Increased renal parameters- urea & creatinine	1	2.5
Hyperkalemia	1	2.5
Raised Bilirubin	1	2.5
Raised LDH	1	2.5
Hyperglycemia	5	12.5
Hypothyroidism	1	2.5
Raised ASO titres	3	7.5
Proteinuria	2	5
Hematuria	1	2.5
Raised CRP	5	12.5
RF	1	2.5
ANA	1	2.5
ANCA	2	5
Hypocomplementemia	1	2.5
Abnormal chest X-ray	2	5
USG abdomen- PCOS	1	2.5
Abnormality in OGD scopy	1	2.5

The most common abnormality observed was leukocytosis, hyperglycemia and raised ESR, each in 5 patients. ASO titre was raised in 3 patients. Proteinuria was seen in 2 patients and hematuria in 1 patient. Autoantibodies such as ANA and Rheumatoid factor were each positive in one patient. ANCA was positive in 2 patients, cANCA was positive in one patient and pANCA was positive in the other patient. Increased renal parameters, hyperkalemia, raised Bilirubin, raised LDH, hypothyroidism, hematuria and hypocomplementemia were positive in one patient each.

Chest x-ray in one patient showed multiple rib fractures with lung contusion on the right side and in another showed multiple lung cavities. In the latter patient, diagnosis of tuberculosis was made. Sputum for acid fast bacilli was negative. Later she was found to have elevated cANCA and diagnosed with GPA. One female patient who was on treatment for infertility had polycystic ovaries on abdominal ultrasonography. A 12 year old girl who presented with purpura followed by severe epigastric pain underwent oesophago-gastro duodenoscopy (OGD scopy) and was diagnosed with a large hiatus hernia. Renal biopsy was performed in one patient with raised renal parameters which showed minimal

mesangial proliferation with two glomeruli showed crescent formation. Immunofluorescence report showed intense positivity for IgA and negative for IgG, IgM. Weak positivity for fibrinogen and C3 - Picture suggestive of HSP nephritis.

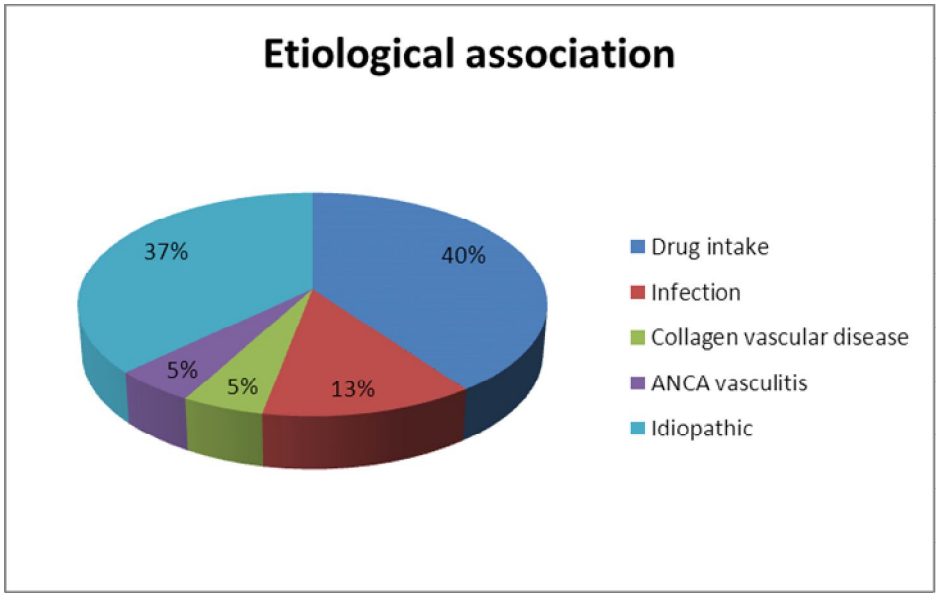
11. Etiological diagnosis

An attempt was made to give an etiological diagnosis to the patients based on the clinical history, examination and investigations. 16 cases (40%) occurred following drug intake and in 5 cases (13%), an infectious etiology was considered. Collagen workup was positive in 2 cases (5%) although none of them showed overt signs of collagen vascular disease. ANCA positive vasculitis was detected in 2 patients (5%). Malignancy was not detected in any patients and 15 cases (37%) of cases were found to be idiopathic.

Table 11 : Etiological association

Etiology	No of cases	Percentage %
Drug	16	40
Infection	5	13
Collagen vascular disease	2	5
ANCA vasculitis	2	5
Idiopathic	15	37

Chart 9 : Etiological association



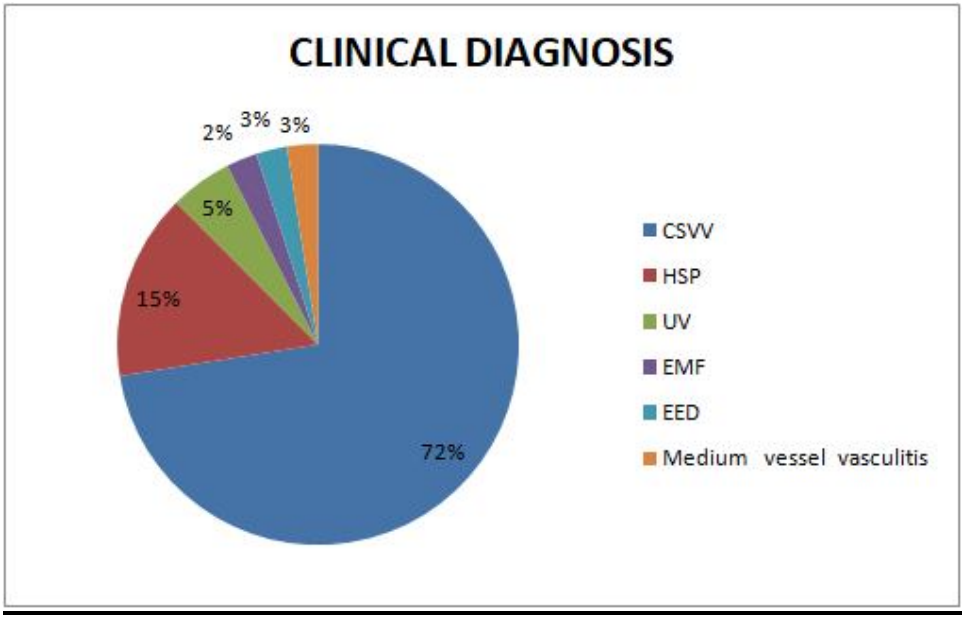
12. Clinical diagnosis

Of the 40 patients, a clinical diagnosis of CSVV was made in 29 patients. HSP was considered in six patients. Two patients had weals lasting for more than 24 hours and another presented with erythema multiforme like lesions. One patient had erythematous plaques over the hands and foot in whom a diagnosis of erythema elevatum diutinum was considered. Severe systemic manifestations with involvement of lung was present in one patient in whom medium vessel vasculitis was suspected.

Table 12 : Clinical diagnosis

Clinical diagnosis	n=40	Percentage %
CSVV	29	72.5
HSP	6	15
UV	2	5
EMF	1	2.5
Erythema elevatum diutinum	1	2.5
Medium vessel vasculitis	1	2.5

Chart 10: Clinical diagnosis



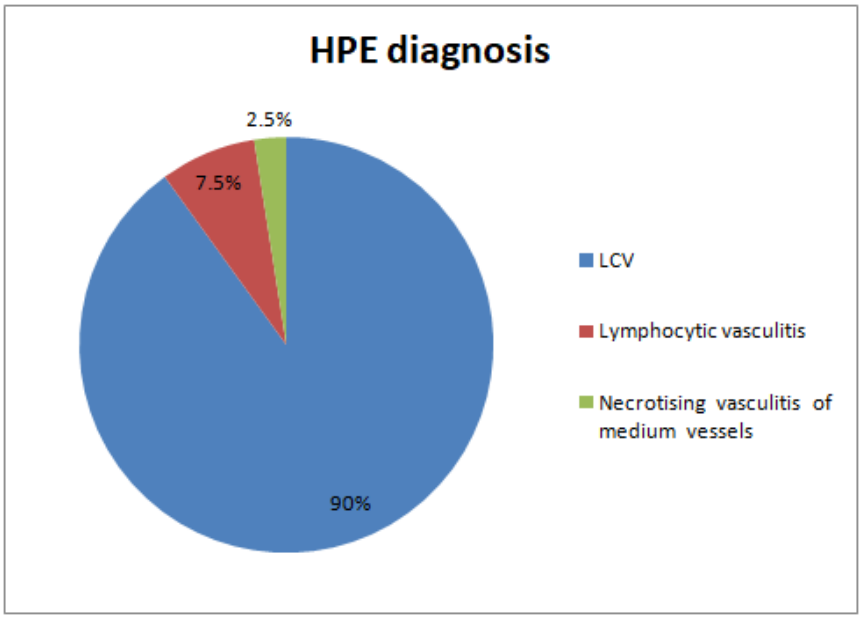
13. Histopathological diagnosis

Based on the histopathological findings, 36 patients were offered a diagnosis of leukocytoclastic vasculitis, 3 patients showed lymphocytic vasculitis. Necrotising vasculitis of medium vessels in subcutis were noticed in one patient.

Table 13. Histopathological diagnosis

HPE diagnosis	n=40	Percentage
LCV	36	90
Lymphocytic vasculitis	3	7.5
Necrotising vasculitis of medium vessels	1	2.5

Chart 11: Histopathological diagnosis



14. Clinicopathological correlation

Of the 29 patients diagnosed clinically as CSVV, 27 patients showed leukocytoclastic vasculitis in biopsy. The other two patients showed lymphocytic vasculitis.

Out of 6 patients who were diagnosed with HSP clinically, all of them showed features of LCV. One of them had raised urea, creatinine with positive pANCA suggestive of Microscopic polyangiitis (MPA). The patient who was diagnosed with medium vessel vasculitis showed necrotising vasculitis of medium arteries of deep dermis and subcutis.

Table 14 : Clinicopathological correlation

Clinical diagnosis (number of cases)	**Histopathological diagnosis (number of cases)**
CSVV (29)	LCV (27) + LV (2)
HSP (6)	LCV (6)
Medium vessel vasculitis(1)	Necrotising vasculitis (1)
Urticarial vasculitis (2)	LCV (1), LV (1)
Erythema elevatum diutinum (1)	LCV (1)
Erythema multiforme (1)	LCV (1)

As shown above, of the two patients who were diagnosed as urticarial vasculitis, one had lymphocytic vasculitis and the other showed LCV. Both of them had normal levels of complement. Patients who were diagnosed showed plaques lesions (EED) and EMF-like lesions also had LCV in histology.

15.Direct immunofluorescence findings

DIF was done in all the patients from the lesional skin . The type of skin lesion from which DIF was taken varied according to the presentation. It was taken from the primary lesion. Palpable purpura was chosen in the majority of patients who presented with it. In others - urticarial lesions, plaque lesion and EMF like lesion were chosen in the remaining patients.

Out of 40 patients, 25 were positive (62.5%) for blood vessel immunoreactive staining in our study. The following table depicts the nature of deposits among the 25 patients.

Table 15 : Distribution of Direct immunofluorescence patterns among the various vasculitis

Diagnosis	Total no of patients	DIF positive	C3	IgM	IgA	IgG
CSVV	30	20	20	11	1	1
UV	2	1	1	1	-	-
HSP	5	4	1	2	4	-
MPA	1	-	-	-	-	-
EED	1	-	-	-	-	-
GPA	1	-	-	-	-	-
TOTAL	40	25	22	14	5	1

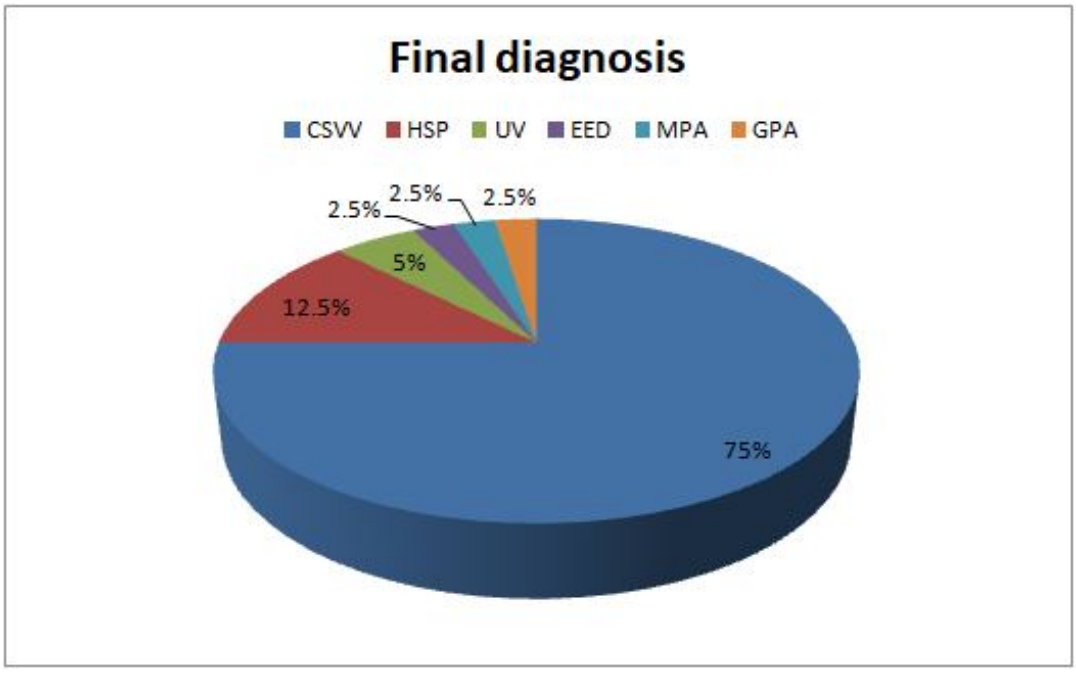
FINAL DIAGNOSIS

The final diagnosis was arrived from correlating clinical, histological and laboratory investigations.

Table 16 : Clinical, pathological and laboratory correlation

Clinical diagnosis (number of cases)	HPE diagnosis (number of cases)	Supportive investigation (number of cases)	Final diagnosis (number of cases)
CSVV (29)	LCV (27), LV (2)	DIF positive (20)	CSVV (29)
HSP (5)	LCV (5)	DIF with IgA deposits (4)	HSP (5)
HSP(1)	LCV (1)	pANCA positive (1)	MPA
Medium vessel vasculitis(1)	necrotising vasculitis (1)	cANCA positive cavities lung (1)	GPA
Urticarial vasculitis (2)	LV (1) LCV (1)	Normal complement levels (2)	Urticarial vasculitis(2)
Erythema elevatum diutinum (1)	LCV (1)	-	EED (1)
Erythema multiforme (1)	LCV (1)	positive DIF (1)	CSVV (1)

Chart 12 : Final diagnosis



COLOUR PLATES

Fig 1 : Palpable purpura

Fig 2 : Palpable purpura

Figure 3 : Palpable purpura extending on to the thigh

Fig 4 : Purpura with hemorrhagic vesicles

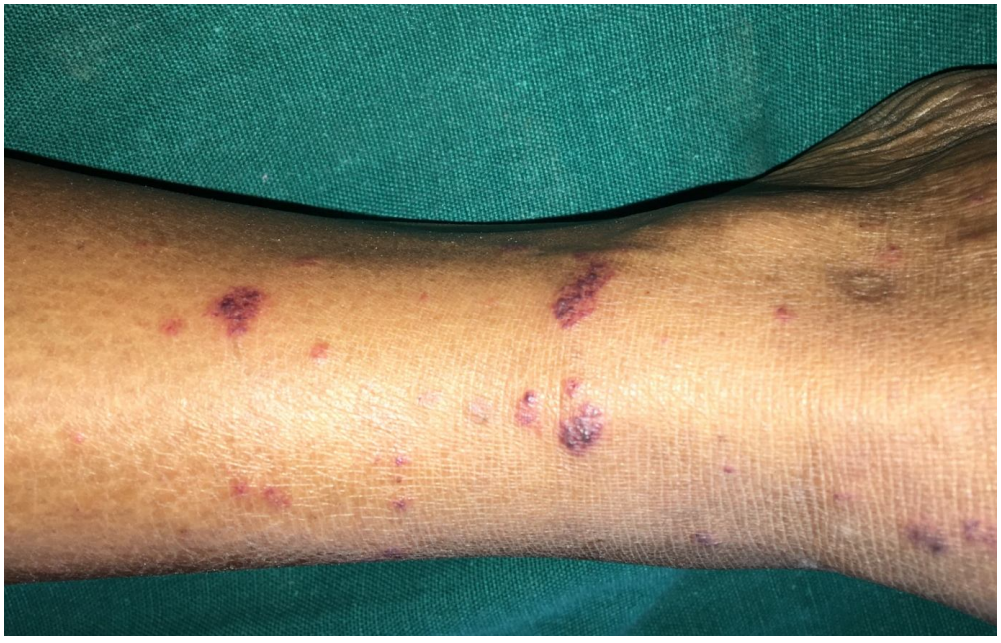


Fig 5: Ulceration on a backgroung of purpura

Fig 6: Patient with multiple large ulcers

Fig 7 : Patient with urticarial vasculitis over the gluteal region and thigh

Fig 8a: Chronic plaques of Erythema elevatum diutinum

Fig 8b : EED

Fig 8c: EED

Fig 9 : Leukocytoclastic vasculitis

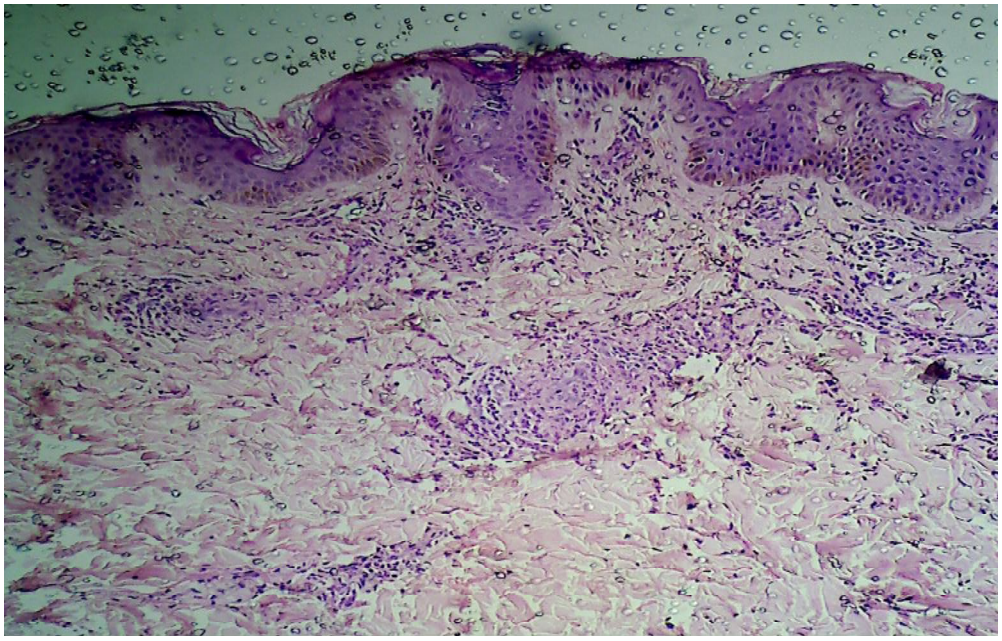


Fig 10 : LCV with neutrophilic debris

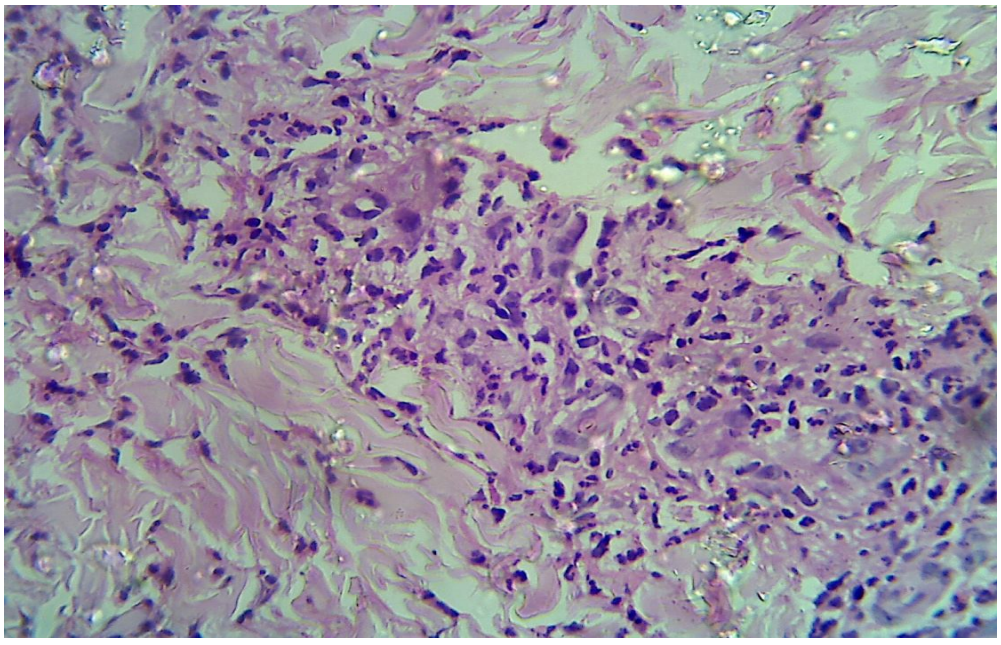


Fig 11 : LCV with fibrinoid necrosis and infiltration

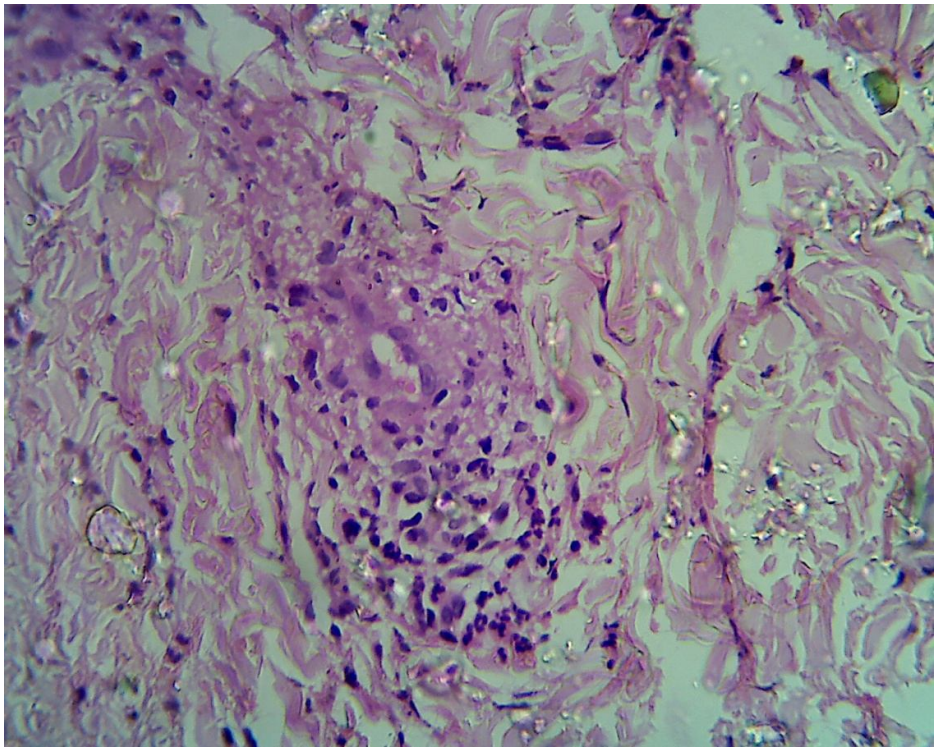


Fig14 : Lymphocytic vasculitis

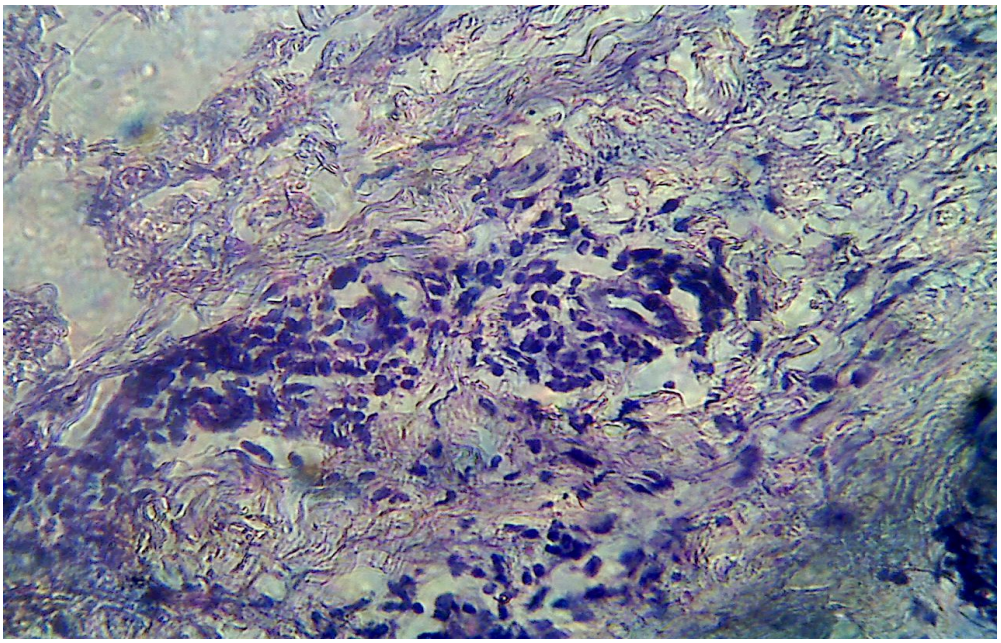


Fig 12: Granulomatosis with polyangiitis (GPA)

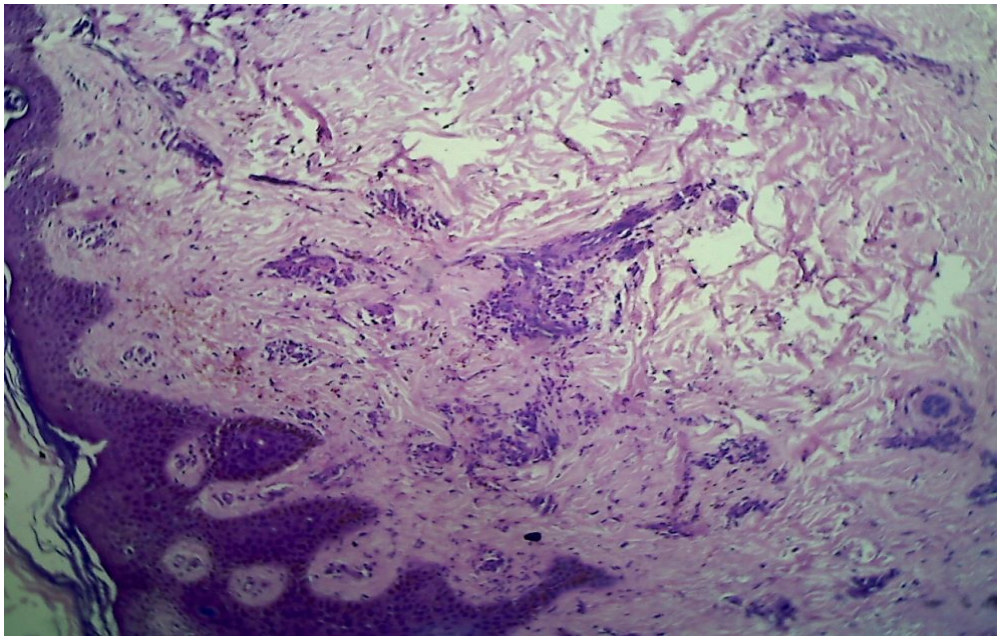
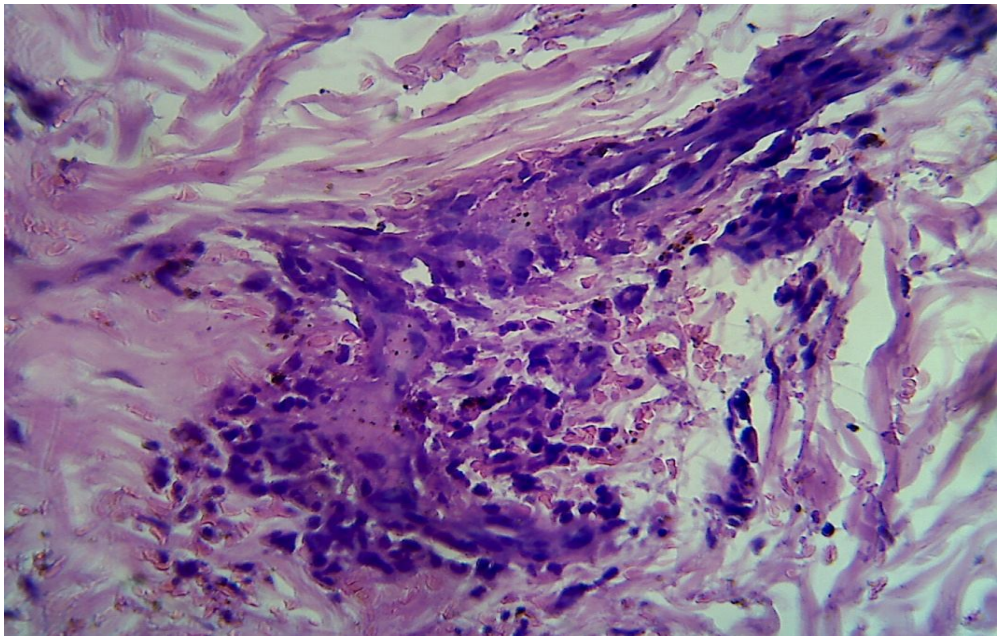


Fig13 : Necrotising vasculitis of GPA



DISCUSSION

Vasculitis is a heterogenous group of inflammatory disorder characterised by a wide array of clinical manifestations ranging from benign, single episode vasculitis to severe, recurrent and life threatening disease. It can occur as a primary phenomenon or secondary to disorders such as drug intake, connective tissue disorders, infections and malignancies. The identification of systemic involvement and underlying precipitating factors, if any, becomes essential with the help of appropriate investigations. The presence of more than one proposed precipitating factor in the same patient makes it hard to attribute the presentation to one factor as the cause.

In our study, we have analysed the clinical features, relevant past history and various laboratory tests to arrive at a diagnosis. This was approached further with skin biopsy and the results correlated with clinical diagnosis. Our study throws light over few newer concepts and confirms the established facts of vasculitis.

The age of presentation in our study varied from 11 to 68 years (Mean - 33 years). In the study by Sais et al [75] , the age was in the range-14- 89 (mean-51 years) and in the study by Ekenstam et al [76] , it was 1- 86 years (mean- 44.8 years). Gupta et al[77] reported a age range of 5- 67 years.

Table 17 : Comparison of gender distribution with other studies

Studies	Male	Female
Our study	24 (60%)	16 (40%)
Sais et al	71 (44.4%)	89 (55.6%)
Gupta et al	20 (40%)	30 (60%)
Ekenstam et al	31 (37.8%)	51 (62.2%)

The age and sex distribution pattern in our study and in the previous mentioned studies reveals that the initial presentation of vasculitis shows no predilection for any particular age or sex group.

The most common skin lesion in our study was palpable purpura which was seen in 95% of cases. Palpable purpura was also the most common presentation observed by others. The most common site involved was lower limbs extending upto thigh and

buttock. Spreading of purpura to abdomen also involved the upper limbs and it occurred in 11 patients in our study.

The second most common primary lesion was hemorrhagic vesicles seen in 30% of patients. This was followed by confluent purpura in 12.5%, urticarial-like plaques in 5%, erythematous plaques over the extremities and EMF-like lesions in 2.5% each. Necrosis and ulceration which were considered as secondary lesions were seen in 30% of cases. All the above lesions were most commonly observed in lower limbs especially in lower two-thirds of legs. Most of the patients had only one type of skin lesion (60%) but in 16 patients (40%) more than one type of lesion was observed.

Table 18 : Incidence of skin lesions in various studies compared to our study

	Our study	**Sais et al**	**Ekenstam et al**
Purpura	95%	89.2%	62.1%
Urticaria like	5%	8.2%	20.1%
Confluent purpura	12.5%	44.6%	-
Ulcers	30%	20.3%	-
Plaques	2.5%	6.09%	-

Systemic manifestations were seen in 19 patients (47.5%) in our study. The most common systemic involvement was found to be arthralgia found in 30% of cases. Knee joint was the most commonest joint involved in 8 out of 12 patients. It was of acute onset and associated with skin lesions. It was neither associated with any other previous illness nor with age related changes. The second most common systemic involvement was abdominal pain seen in 20% of patients. Vomiting, diarrhoea, loss of consciousness and chest pain with breathlessness was found in one patient each.

Table 19: Comparison of systemic symptoms with other studies

	Our study	**Sais et al**	**Ekenstam et al**
Fever	7.5%	31.6%	15.8%
Arthralgia	30%	36.7%	42.6%
Abdominal pain	20%	9.5%	9.7%
Dysnoea	2.5%	7%	3.6%

Additional symptoms seen in our study are vomiting, diarrhoea, loss of consciousness and loss of weight. They were all reported in one patient each. Four patients had both abdominal pain and arthralgia in whom a clinical diagnosis of HSP was made.

In our study, sixteen (16) patients had given history of intake of drugs for illnesses that had occurred prior to the onset of vasculitic lesions. The commonly consumed drug in our study was antibiotics seen in four patients (12.5%) . This is comparable with study done by Ekenstam et al in which the incidence of drug intake was 9.7% and the most commonly consumed drug was antibiotics. The second common in our study was analgesics and oral hypoglycemics agents in three patients each. Antihistamines, Tamoxifen, ATT and Thyroxine in one patient each. Two patients were taking drugs, details of which were unknown. One of them was taking drugs for the treatment of infertility.

History of infectious illness in the recent past was seen in 5 (12.5%) patients in our study. This incidence is comparable with Ekenstam et al study which showed an incidence of 9.7%. In our study, two (5%) patients had suffered from upper respiratory tract infection, one had otitis externa and another had bilateral chronic otitis media. All the above mentioned patients had taken antibiotics as treatment. Therefore the etiological association could not be ascertained in these cases.

Out of 40 patients in our study, 9 patients had similar skin lesions in the past. Of the 9 patients with recurrence, 7 had the illness for less than 6 months. Vasculitis that is limited to a period of 6 months is considered to be acute and are typically associated with a drug or infectious trigger in about 60% of cases[CArlson]

Eight out of forty patients in our study had an associated non infectious medical illness. They were :

1. Bullous pemphigoid
2. Hypothyroidism
3. Carcinoma of Breast
4. Polycystic ovarian disease
5. Atopy
6. Peripheral sensory neuropathy
7. Hiatus hernia

8. Bilateral facial palsy

The associations appear to be incidental and their significance is not known.

Etiological association was suspected in 63% of our patients. This is comparable to studies by Gupta et al in which etiological association was suspected in 74% of patients and in 67.2% by Sais et al. The most common cause implicated was drug intake (40%) followed by infection in 13% of patients in our study. Gupta et al reported drug-induced vasculitis in 50% and an infectious etiology in 10%. These figures are also comparable to our study.

Table 20 : Comparison of etiological spectrum between studies

Etiology	our study	Gupta et al	Sais et al	Ekenstam et al
Drug intake	40%	50%	9.6%	9.75%
Infection	13%	10%	28%	9.75%

The most common blood parameter abnormality observed in our study was leukocytosis, hyperglycemia and raised ESR, each of them in 5 patients (12.5%) indicating an ongoing active inflammation. Sais et al observed a raised ESR in 52.4% and leukocytosis in 18%. ASO titre was raised in 3 patients in our

study. Though it was observed in patients different from those who had suffered from pharyngitis.

Abnormal renal function in the form of proteinuria was seen in 2 patients (5%) and hematuria in 1 patient (2.5%). Increased serum urea, creatinine and electrolyte abnormalities (hyperkalemia) were observed in one patient each. The patient with raised RFT was later found to be pANCA positive suggesting an ANCA vasculitis. The incidence of renal involvement was very less in our study when compared to the Sais et al study in which raised urea and creatinine was observed in 26% and urine abnormalities in 21.1%.

Collagen vascular disease in the form of detection of autoantibodies such as ANA and Rheumatoid factor revealed positivity in one patient each (2.5% each). None of the patients showed overt features of collagen vascular diseases. ANA and RA were positive in 28.5% and 26.4% in the study by Sais et al and were also related to collagen vascular disease. ANCA was positive in 2 patients in our study, one patient was cANCA positive and the other was pANCA positive. Abnormal liver parameters, hypothyroidism and hypocomplementemia were seen in one patient

each - 2.5%. Decrease in complement levels was seen in a patient with severe HSP nephritis.

Chest x-ray was found to be abnormal in 2 patients. One patient showed multiple rib fractures with lung contusion on the right side which was secondary to a road traffic accident and another showed multiple thin walled cavities who presented with respiratory failure. The patient was diagnosed of tuberculosis and started on ATT. Later was found to have elevated cANCA and diagnosed with GPA.

Renal biopsy was performed in one patient with raised renal parameters which features suggestive of HSP nephritis.

Table 21 : Investigations - compared to other studies.

Investigations	**Our study %**	**Sais et al%**	**Ekenstam et al%**
Leukocytosis	12.5	52.4	-
Increased renal parameters- urea & creatinine	2.5	10	83
Raised Bilirubin	2.5	-	5.8
Raised ASO titres	7.5		
Proteinuria	5	19	-

Hematuria	2.5	-	7.3
RF	2.5	26.4	28
ANA	2.5	28.5	20.6
ANCA	5	21	-
Hypocomplementemia	2.5	25	3
Abnormal chest X-ray	5	-	8.3

Of the 40 patients in our study, a clinical diagnosis of CSVV was made in 29 patients, who had no associated systemic symptoms and abnormality in the workup. HSP was considered in six patients who presented with palpable purpura and associated systemic features such as joint and abdominal pain and 2 of them had abnormal renal parameters. One patient had painful urticarial-like lesions over the trunk and lower limbs that persisted for about 3-5 days to leave a post inflammatory hyperpigmentation in whom a diagnosis of urticarial vasculitis was considered. Another patient presented with erythema multiforme-like lesions more over the extremities. EED was suspected in a patient with few erythematous plaques and many fibrotic nodules over the palms, soles and few over the trunk. Severe systemic manifestations were present in one patient along with purpura and large ulcers, in whom a medium vessel vasculitis was suspected.

Histology showed features of leukocytoclastic vasculitis in 36 (90%) patients. Lymphocytic vasculitis was seen in 3 (7.5%) patients. Gupta et al observed a slightly lower incidence of LCV - 72% and lymphocytic vasculitis in 12% of cases. Necrotising vasculitis(GPA) involving the medium vessels of the deep dermis and subcutaneous tissue was seen in one patient .

In our study, DIF was positive in 62.5% of patients which is comparable to study by Kulthanan et al[78] with 76% positive DIF and 96% in studies by Grunwald et al [79] and Mackel et al[80] . Of the 30 CSVV patients, around 66% showed positive DIF. All of them had C3 deposits and 55% (11 out of 20 patients) of them had IgM deposits. In HSP vasculitis, 4 out of 5 patients had predominant IgA deposits. DIF was positive in one patient out of 2 patients with urticarial vasculitis. The most common immunoreactive deposit in all the studies was C3. The next most common was IgM similar to other studies.

In cases clinically diagnosed with CSVV, the diagnosis was confirmed by absence of systemic features suggestive of other organ involvement and absent laboratory or imaging abnormalities [81] . They constituted 75% of cases in our study. Among the cases

of CSVV, those with history of drug intake / infection are also known as hypersensitivity vasculitis or allergic vasculitis.

The diagnosis of HSP was based on the presence of purpura predominantly over the lower limbs and presence of one of the following 4 features [82] .

1. Abdominal pain
2. Arthritis / arthralgia
3. Abnormal renal function - hematuria, proteinuria etc
4. LCV / Proliferative glomerulonephritis with predominant Ig A deposition in renal biopsy

Of the six cases clinically diagnosed (purpura, arthralgia / abdominal pain) as HSP, all 6 showed LCV in histology, 3 had abnormal renal parameters and 4 patients had positive DIF. One of them had severe renal involvement and renal biopsy was carried out which showed predominant deposits of Ig A and mesangial proliferation suggestive of HSP. One patient had large ulcers on a background of purpura, showed high titres of pANCA positivity with raised renal parameters suggestive of microscopic polyangiitis.

Among the 3 patients with histopathological findings of lymphocytic vasculitis, 2 had clinical presentation of palpable purpura and 1 had a clinical picture of urticarial vasculitis . The histological picture of lymphocytic vasculitis has been commonly reported in collagen vascular disorders followed by urticarial vasculitis [83] . In other 2 patients who presented with palpable purpura, this picture might be explained delayed timing of presentation and biopsy (>48 hours) [84] .

Two other patients clinically diagnosed as UV and EED (1 patient) and EMF (1 patient) also showed leukocytoclasia with no other abnormality in other parameters.

One young female patient who presented with bilateral CSOM, facial palsy and respiratory failure who was suspected to have medium vessel vasculitis showed multiple cavities in the lung, high titres of cANCA positivity and necrotizing vasculitis of medium vessels. A diagnosis of Wegener's granulomatosis was made. The patient expired within a few days.

On correlating the clinical, laboratory and histopathological features, 5 different diagnosis was arrived at in our study.

The final diagnosis in percentage is as given below

Table 22 : Final diagnosis

Final diagnosis	Percentage
CSVV	75%
HSP	12.5%
UV	5%
EED	2.5%
MPA	2.5%
GPA	2.5%

SUMMARY

A descriptive study on the clinicopathological correlation of cutaneous vasculitis was done from June 2016 to May 2017. Patients who presented with skin lesions and systemic symptoms suggestive of vasculitis were included in the study. A thorough history, clinical examination, blood work up, imaging and histopathological examination was done and a final diagnosis was made. The incidence of each parameter was recorded, analysed and compared with other studies.

- Our study included 40 patients with skin lesions suggestive of vasculitis. There were 24 males and 16 females.
- Mean age of patients in our study was 33 years
- Skin only involvement was seen in 52.5% of patients.
- The most common cutaneous manifestation was palpable purpura followed by hemorrhagic vesicles, ulcers and weals.
- Systemic involvement was seen in 47.5 % of patients. The common systemic manifestations observed were fever, arthralgia and abdominal pain.

- The most common laboratory abnormality observed was leukocytosis and raised CRP suggesting an ongoing inflammation.
- Renal involvement was seen in 7.5% patients in the form of raised urea and creatinine, hematuria and proteinuria
- Lung involvement in the form of multiple cavitating nodules with respiratory failure was seen in 1 patient with Granulomatosis with polyangiitis.
- Cutaneous small vessel vasculitis (without systemic involvement) constituted the majority of cases - 75%
- HSP vasculitis was the second most common vasculitis observed was 12.5%.
- ANCA positive vasculitis constituted 5% of cases in our study.
- Normocomplementemic urticarial vasculitis comprised of 5% of cases
- Erythema elevatum diutinum was diagnosed in 1 patient (2.5%)
- One patient who was diagnosed with Granulomatosis with polyangiitis succumbed to the illness.

CONCLUSION

Cutaneous vasculitis with its myriad clinical presentations remains a diagnostic and therapeutic challenge. Accurate diagnosis depends on a stepwise and systematic evaluation of the patient. This begins with the fundamentals of history and clinical examination; and progresses to histopathological examinations and laboratory studies. With the extent of scientific progress seen in the areas of immunology research, it is likely that vasculitis may enter the realm of personalised medicine [85] . Examples towards this trend is the identification of a number of genes which are strongly associated with specific vasculitis (For example HLA DRB1*04 is associated with Giant cell arteritis) and development of targeted therapies.

With all this progress comes the cost of expensive investigations and treatment. This is likely to place strain on the finances of the health system. This precisely was one of the challenges that we faced in our study, as mentioned subsequently in the study limitations section.

The experience gained from this study helped us to rely more rationally on clinical and histopathological features in arriving at a

specific diagnosis. Special laboratory investigations were diligently used only in special circumstances.

Limitations of the study:

1. As the study was a cross-sectional observational study, follow-up data was not available in a few cases.
2. The study sample size was small
3. Due to lack of certain facilities, expensive investigations (such as autoantibody testing) could not be done in all patients.

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PROFORMA

Name :

Age/Gender:

PIN No:

Address

Phone number

Occupation :

Presentation

Purpura for ……..DURATION	Palpable- /blanching- /pain-
	Site: Sparing of intertriginous areas- yes/no
	Ecchymosis /Haemorrhagic vesicles
Necrosis and Ulcer-	
Deep nodules	
Broken livedo reticularis/ urticaria	

Systemic :

General	Weight loss, fever, fatigue,Anorexia	
Musculoskeletal	Arthralgia, myalgia ,arthritis	

Abdominal	Abdominal pain Blood in stools	
Mucosal	Dry eyes or mouth,	
	Oral or nasal ulcers	
CVS	Chest pain/ dyspnoea/ cough with hemoptysis	
CNS	Blackouts	
	Paraesthesias, numbness, psychiatric symptoms	
Renal	Colour, quantity of urine	
RS		

Others:

BLEEDING DIATHESIS	
DRUG INTAKE / INSULIN	
ALLERGIES	FOOD/DRUGS
ANT BITE / EXERCISE	
INFECTIONS OR ILLNESS	
HEPATITIS/JAUNDICE	
Suggestive of SLE / Behcet / RA Or Inflammatory Bowel disease	
Neutrophilic disorders- PG (as in EED)	

Exposure to chemicals :

Similar lesions in the past? Yes or No

Pattern of recurrence

Interval between episodes

Precipitating factors if any -

Seasonal variation -

Treatment history:

Past history :

DM/ HT / asthma / other allergies / TB / Epilepsy / connective tissue illness / HIV

Other skin disorders :

Others-

Personal history: Smoker / Alcoholic /

Family history :

O/E:

General- pallor, icterus / LN, PE

CVS / RS / ABD

Head to toe : eyes, nose, mouth and palate, UL, nails,

Skin-

Investigations:

CBC	**RFT**	**LFT:**
HB- ,MCHC-	UREA-	BILIRUBIN
TC-	CR-	OT
DC-	Na-	PT
PLT-	K-	ALP
MCV-		
BT / CT		
ESR		

ASO	URINE ROUTINE-	CXR
CRP		USG ABD
RF		
DIF		
HBsAg		
HCV		
ANA		
ANCA		
Peripheral smear		
Infection and malignancy screen		
Others:		

Biopsy – (HPE number - …….)

CONSENT FORM

I Mr/Mrs _____ hereby volunteer to participate in the study "**CLINICOPATHOLOGICAL CORRELATION OF CUTANEOUS VASCULITIDES** " . I was completely explained about the nature of the study by the doctor, knowing which I fully give my consent to participate in this study. I also give consent to take clinical photographs for the purpose of this study.

Date:

Place: Signature of the Patient/Guardian

xgGjy gbtk

ngaH : taJ :

ghypdk :

Kfthp :

muR Nfhit kUjJtf fyY}hpapy Njhy kUjJtj Jiwapy (gll NkwgbgG gapYk khztp **kU. fpU#]z kpuh** mthfs Nkwnfhs Sk **“,ujjf; FHhafspy; VwgLk; xt;thik”** Matpd nraKiw njhlhghd midjJ tpguqfisAk NflL VdJ reNjfqfisj njspTgLjjpf nfhzNld

.

ehd ,ej Matpy vdid / vd Foeijia ghpNrhjid nraa KO kdJlDk RarpeNidAlDk rkkjpffpNwd. vd/vd Foeijapd Neha gwwpa ,ej Matpy vqfsJ midjJ tpguqfSk ghJfhffggLJld Neha gFjpapd Gifgglk kwWk,jd KbTfs Matpjopy ntspaplggLtjpy Ml-Nrgid ,yiy vdgijj njhptpjJfnfhsfpNwd. vej Neujjpyk ,ej Matpypueh ehd tpyfpfnfhss vdfF chpik czL vdgijAk mwpNtd.

,lk : Nehahsp/ Foeijapd ngwNwhh

ehs : myyJ ghJfhtyh ifnahggk.

KEY TO MASTER CHART

PP	-	Palpable purpura
HV	-	Hemorrhagic vesicles
CP	-	Confluent purpura
MT	-	Metformin
GP	-	Glimepiride
BP	-	Bullous pemphigoid
CPS	-	Cephalosporins
B/L	-	Bilateral
PE	-	Pedal edema
BR	-	Bilirubin
ALP	-	Alkaline phosphatase
SGOT	-	Serum glutamic oxaloacetate transaminase
SGPT	-	Serum glutamate pyruvate transaminase
LOC	-	Loss of consciousness
Cr	-	Creatinine
Al	-	Albumin
LC	-	Leukocytosis
HT	-	Hypertension
DM	-	Diabetes
AH	-	Antihistamines
AN	-	Analgesics
NP	-	Neuropathy

Yrs	-	Years
Dia	-	Diarrhoea
Vom	-	Vomiting
Sx	-	Surgery
HH	-	Hiatus hernia
IF	-	Infertility
Rx	-	Treatment
Sen	-	Sensory
LOW	-	Loss of weight
D	-	Days
Mn	-	Month
NK	-	Not known
BL	-	Bullous lesions
Epi	-	episodes
APT	-	Appendicectomy
LC	-	Lung cavities
NV	-	Necrotising vasculitis
K	-	Potassium
HT	-	Hypothyroid
HG	-	Hyperglycemia

S.NO	AGE	SEX	PIN NO	PP	PURPURA DISTRIBUTION		OTHER SIGNS	SYSTEMIC SYMPTOMS								DURATION	RECURRENCE	PAST HISTORY	DRUG HISTORY	co morbidities	CBC & PS	RFT(urea, cr)	LFT(Bilirubin, SGOT,SGPT,ALP)	URINE ROUTINE(ALBUMIN, SUGAR, RBC	INFECTION SCREEN(ASO, HbsAg, HCV,	AUTOANTIBODIES(c-ANCA, p-ANCA, ANA, RF)	IMAGING STUDIES(CXR, USG Abd)	BIOPSY	DIF				DIAGNSIS
					LL	UL	HV	ulcers	CP	plaques	weals	EMF Like	abd pain	fever	joint pain	others	in case											INFERENCE	C3	IgM	IgA	IgG	
1	15	M	11990	+	+	+							+			LOC& vom		15 days		_			N	N	N	N	N	N	N	LCV	+	+			CSVV
2	22	M	432046	+	+	+												1 mn					N	N	N	N	+ ASO	N	N	LCV					CSVV
3	25	F	479100	+	+	-							+	+				15 days					N	N	N	N	N	N	N	LCV	+	+	+		CSVV
4	55	M	408733		+	+				+								10 years	1 week	BL - body	steroids for BP	BP	N	N	N	N	N	N	N	LCV					**EED**
5	17	M	475371	+	+	-	+	+										6mns	4th epi	atopy			N	N	N	N	N	N	N	LCV					CSVV
6	11	F	519243	+	+	-												2 days		similar lesions 6 mns			N	N	N	N	N	N	N	LCV	+	+			CSVV
7	42	F	560550	+	+	-	+	+					+					15 days					N	N	N	trace alb	+ CRP	N	N	LCV	+	+	+		**HSP**
8	19	M	579984	+	+	-												1 Week					N	N	N	N	+ ASO +	N	N	LCV					CSVV
9	38	M	629021	+	+	-		+						+		Dia		15 days					N	N	N	N	N	N	N	LCV	+				CSVV
10	23	M	629737	+	+	-	+	+										1 mn			T.MT and T.GP	DM	LC	N	N	N	+ CRP	N	N	LCV					CSVV
11	28	M	588116	+	+	-	+	+					+					15 days					LC,PS-	raised	N	N	N	pANCA +	N	LCV					**MPA**
12	25	M	641871	+	+	-									+			2 days					N	N	N	N	CRP- +	RF- +	N	LCV	+				CSVV
13	28	M	652164	+	+	-									+			10 days		RTA one mn ago	CPS and AN-		N	N	N	N	N	N	lung contusion	LCV	+	+		+	CSVV
14	12	F	347890	+	+	-												2 days					anemia	N	N	N	N	N	N	LCV	+	+			CSVV
15	17	M	710854	+	+	-												3 weeks					N	N	N	N	N	N	N	LCV					CSVV
16	42	M	712921	+	+	+			+						+			20 days		urine dribbling- 1day			N	N	N	N	+ ASO	N	N	LCV	+				CSVV
17	38	M	57553	+	+	-	+	+							+			1 week		urine - pink	AN	DM	LC & HG	N	BR - 3.3	N	N	N	N	LCV	+	+			CSVV
18	42	M	762059	+	+	+			+									15 days		ear infection- 20 days	CPS		N	N	N	N	N	N	N	LCV					CSVV
19	45	M	49914	-	-	-					+				+			10 days			AH		LC	N	N	N	N	N		LCV	+	**+**		**+**	**UV**
20	35	M	794004	+	+	-		+					+		+	vom		3 days	one mn-3rd epi				N	N	N	N	N	N	N	LCV					**HSP**
21	30	F	874983	+	+	+	+	+	+						+			2mns	+, once in 2	pharyngitis past 3 days	NT		HG	N	N	Sugar +	N	N	N	LCV					CSVV
22	30	F	819530	+	+	+								+	+	PE		25 days		Rx for IF	NT		N	N	N	N	N	N	PCOS	LCV	+	+			CSVV
23	20	M	603582	+	+	+										b/l CSOM,	DYSPNEA	2 days		LOW	Abs		N	N	N	N	N	CANCA	B/L CSOM & LC	**NV**					**GPA**
24	50	M	48989	+	+	-		+										1 Week		sen NP			N	K- 7.7	LDH-	N	N	N	N	LCV	+				CSVV
25	48	F	734883	+	+	-	+	+										3 mns	+, 25 , 2 Yrs		TRX&OHAs	HT	N	N	N	N	N	N	N	LCV	+	+			CSVV
26	19	F	89438	+	+	-							+			vom		10 days	once in 6mns-	HH			N	N	N	N	N	ANA- +	HH	LCV			**+**		***HSP***
27	40	M	737624	+	+	-			+						+			10 days					N	N	N	N	N	N	N	**LV**	+	+			CSVV
28	31	F	738308	+	+	-																	N	N	N	N	CRP- +	N	N	LCV	+				CSVV
29	55	M	67456	+	+	-	+	+								PE		1mn			T.MT 500mg		N	N	N	N	N	N	N	LCV	+	+			CSVV
30	38	M	58340	+	+	-							+		+	eczema		10 days				DM	raised ESR	N	N	SUGAR - +	N	N	N	LCV	+				CSVV
31	40	F	1005720	-	+	+					+							4 mns	once in 20 d		AHs and Abs		N	N	N	N	N	N	N	**LV**					**UV**
32	25	M	880969	+	+	+			+									3mns	+, once a mn	pharyngitis	steriods		N	N	N	N	CRP- +	N	N	LCV	+	+			CSVV
33	50	F	919072	+	+	-												20 days		Sx ca breast- 7 Yrs ago	T.Tamoxifen	DM	N	N	N	sugar -	N	N	N	LCV					CSVV
34	54	M	1123890	+	+	-												10 days					N	N	N	N	N	N	N	LCV	+				CSVV
35	68	M	85158	+	+	+	+											1 Week				DM	N	N	N	N	N	N	N	LCV					CSVV
36	14	F		+	+	-												1 Week	once a mn for 3	cola coloured urine	high dose		N	N	N	Alb - +++,	N	LOW C4-	N	LCV			**+**		**HSP**
37	38	F	1108152	+	+	-									+			10 days					N	N	N	N	N	N	N	LCV	+				CSVV
38	40	F	1113456	-	+	+						+						8 Days		3 epi HSV - 1 yr			N	N	N	N	N	N	N	**LV**	+				CSVV
39	38	F	993863	+	+	-												3 days					N	N	N	N	N	N	N	LCV					CSVV
40	13	F	938290	+	+	+							+		+	vom &dia		8 days		APT	CPS and AN-		N	N	N	N	N	N	N	LCV		**+**	**+**		**HSP**